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CONTENTS OF PREVIOUS NUMBERS

MAY, 1920. NUMBER 5

Scorbutic Beading of the Ribs. Alfred F. Hess, M.D., and Lester J. Unger, M.D., New York.

Water Retention in Pneumonia. Herbert O. Lusaky, M.D., and Hugo Friedstein, M.D., Chicago.

Prenatal Syphilis, with a Plea for Its Study and Prevention. John A. Kolmer, M.D., Philadelphia.

The Antineurotic and Growth Stimulating Properties of Orange Juice. Albert H. Byfield, M.D., and Amy L. Daniels, Ph.D., with the Cooperation of Rosemary Laughlin, M.S., Iowa City.

Fluid Injections in Dehydrated Infants. Stafford McLean and Charles A. Lang, M.D., New York.

The Length of the Large and the Small Intestine in Young Children. Lewis Robbin, M.D., New York.

Treatment of Birth Fractures at Fordham Hospital. Samuel W. Boorstein, M.D., New York.

Craniotabes and Beading of the Ribs as Signs of Rachitis. Herman Schwartz, M.D., New York.

Artificial Infant Feeding: Give the Baby Enough. Maurice Ostheimer, M.D. Philadelphia.

Clinical Department:
Subcutaneous Emphysema in an Infant Three Days Old. Harold K. Faber, M.D., San Francisco.

Progress in Pediatrics:
Review of the Literature of the Past Five Years on Anaphylaxis and Related Phenomena. A. R. Cunningham, M.D., Boston.

JUNE, 1920. NUMBER 6

The Effect of Intravenous Injections of Calcium in Tetany and the Influence of Cod Liver Oil and Phosphorus in the Retention of Calcium in the Blood. Alan Brown, M.D.; Ida F. MacLachlan, B.A., and Roy Simpson, M.B., Toronto.

The Nitrogenous and Sugar Content of the Blood of the New-Born. J. P. Sedgwick, B.S., M.D., and Mildred R. Ziegler, M.S., Minneapolis.

Allergy in Infants and Children. Oscar M. Schloss, M.D., New York.

Fordyce's Disease as Pseudo-Koplik Spots and a Cause of Mistakes in the Diagnosis of Measles. Joseph C. Regan, M.D., Brooklyn.

The Bacillus of Pfeiffer in Inflammations of the Respiratory Tract in Children. Martha Wollstein, M.D., and Ralph C. Spence, New York.

Bullous Eruption Complicating Measles. Frank C. Neff, M.D., Kansas City, Mo.

Clinical Department:
Hemorrhage into the Spinal Cord at Birth. Charles W. Burr, M.D., Philadelphia.

Progress in Pediatrics:
Von Pirquet's Feeding System. Harold K. Faber, M.D., San Francisco.

Index.

JULY, 1920. NUMBER 1

Report of a Case of Malignant Thymoma with Necropsy. Nathan Chandler Foot, M.D., Boston.

Prescriptions for Egg Albumin in Stools. Clifford G. Grulee, M.D., Chicago.

The Hemorrhagic Tendency as a Frequent Cause of Cranial Hemorrhage of the New-Born. John A. Foote, M.D., Washington, D. C.

Active Immunization Against Diphtheria in a Large Child-Caring Institution. Julius Blum, M.D., New York.

The Eye in Hereditary Syphilis. John Green, Jr., M.D., St. Louis.

Review of the Literature of Syphilis in Infancy and Childhood. Part I. Philip C. Jeans, M.D., St. Louis.

AUGUST, 1920. NUMBER 2

The Duct Sign in Mumps. David Murray Cowie, M.D., Ann Arbor, Mich.

Acute Cerebrocerebellar Ataxia, with Report of Cases. J. P. Crozer Griffith, M.D., Philadelphia.

Studies on the Effect of Diphtheria on the Heart. Hugh McCulloch, M.D., St. Louis.

A New Method of Diagnosis of Peritonitis in Infancy and Childhood. Preliminary Report. Bernard Denzer, M.D., New York.

A Study of Pneumonia in Infancy and Childhood During Recent Epidemics. Henry Heiman, M.D., New York.

A Twenty-Four Hour Schedule for School Boys. Richard M. Smith, M.D., Boston.

Clinical Department:
Case of Purpura with Symmetrical Gangrene of the Fingers. May Michael, M.D., Chicago.
Elephantiasis Congenita Angiomatosa (Unna), Associated with Changes in the Capillaries. Milo K. Miller, M.D., and Karl M. Nelson, M.D., Chicago.

Progress in Pediatrics:
A Review of the Literature of Syphilis in Infancy and Childhood. Part II. Philip C. Jeans, M.D., St. Louis.

SEPTEMBER, 1920. NUMBER 3

The Significance of Xanthochromia of the Cerebrospinal Fluid with Report of a Case in a Premature Infant. Isaac A. Abt, M.D., and I. Harrison Timpeer, M.D., Chicago.

Bodily Mechanics. Its Relation to Cyclic Vomiting and Other Obscure Intestinal Conditions. Fritz B. Talbot and Lloyd T. Brown, Boston.

The Circulatory Reactions to Graduated Exercise in Normal Children. May G. Wilson, M.D., New York.

Studies in Spasmophilia. I. Spasmophilia and Vitamins. Ludo von Mysenbug, M.D., Minneapolis.

Further Progress in the Study of the Relative Efficiency of the Different Mercurial Preparations in the Treatment of Congenital Syphilis in Infants and Children as Determined by a Quantitative Analysis of the Mercury Elimination in the Urine.

Clinical Department:
A Case of Priapism Resulting from Rapidly Spreading Myxosarcoma with Generalized Metastases. David Murray Cowie, M.D., Ann Arbor, Mich.

Progress in Pediatrics:
A Review of the Liteurature of 1919 on the Genito-Urinary Diseases of Children. Lewis Webb Hill, M.D., Boston.

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ACROCEPHALY AND SCAPHOCEPHALY WITH SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES *

A STUDY OF THE SO-CALLED "ACROCEPHALOSYNDACTYLISM" *

EDWARDS A. PARK, M.D., AND GROVER F. POWERS, M.D.

BALTIMORE

That acrocephaly and syndactylism occur in combination has been generally appreciated since 1906, when the French pediatrician, Apert,[1] published the report of eight cases discovered in the literature and of one case from personal experience. Inasmuch as all the subjects exhibited deformities of the head, hands and feet so similar as to seem almost identical, Apert believed that the combination constituted a clinical entity. Accordingly, he gave to it the name "acrocephalosyndactylism." Since the publication of Apert's paper, other cases have been reported. We have been able to collect from the literature eleven cases exactly like those in Apert's series, and four others presenting the same deformity of the head but much less extensive deformities of the extremities. In addition, we have found four cases in which there was a characteristic affection of the head with slight malformations of the extremities, probably of the same nature as the malformations in the other cases but in the absence of exact description not proven. Including the cases of Apert's series and the patient who came under our own observation, made the subject of special report in this paper, the total number amounts to twenty-nine. Ten of the twenty-nine cases are reported from England, eight from France, four from Sweden, three from the United States, and one each from Italy, Germany, South America and Denmark. It is remarkable that only one case comes from German sources.

Moreover, we have been able to add to the above series two cases of scaphocephaly with malformations of the extremities, one case found reported in the literature and one from personal observation.

* From the Department of Pediatrics, Johns Hopkins University.

1. Apert, E.: De l'acrocéphalosyndactylie, Bull. et mém. Soc. méd. d. hôp. de Par. **23**: 1310, 1906.

Although the number of cases gathered together is small, we have gained the impression that the occurrence of the kind of defective development of the extremities in association with the kind of defective development of the head is not extremely uncommon. Dr.

Fig. 1.—Photograph of an engraving from an anonymous atlas formerly belonging to the collection of Dr. Friedrich Ahlfeld, Leipzig, now No. 127287 of the Ahlfeld Teratological Collection, the gift of Francis M. Jencks, Johns Hopkins Medical School. It represents a child with acrobrachycephaly and symmetrical deformity of hands. (We are indebted to Dr. P. G. Shipley for the discovery of the engraving.)

John Thomson of Edinburgh recently showed one of us photographs of two patients showing the combination of congenital defects, and the report of the existence of one in Boston and of another in New York has reached us while the present study was in progress.

REPORT OF CASE

D. H., aged 4 years and 8 months, of Jewish parentage, was born May 25, 1915.

Family History.—The father was aged 48 and the mother was aged 28 when the child was born. Both parents have always been well; they present no deformities. The patient is the eldest of three children; the younger two are normal. Parents know of no deformities in members of their respective families.[2]

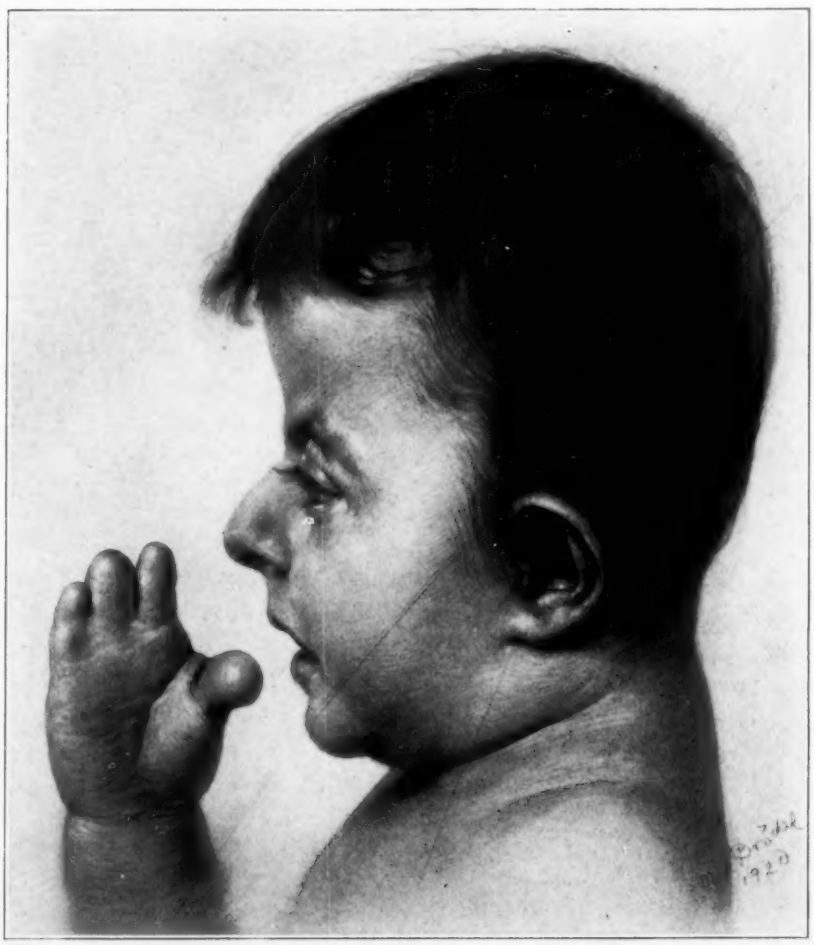

Fig. 2.—D. H. at age of 18 months.

Past History.—The child was born twenty-three days before term. The membranes ruptured six days before birth; the quantity of amniotic fluid discharged was said to have been large; labor began two days before birth.

2. The father has seen his grandparents and one great-grandparent and his five brothers and sisters. The mother has seen her parents, grandparents, and two greatgrandparents. Her seven brothers and sisters and five uncles and aunts were all normal.

Delivery with high forceps; child was cyanosed and not expected to live; scalp severely lacerated; deformities of head and extremities fully developed. The child was nursed for one year; has had no illnesses and has thrived. In April, 1916, at age of 11 months, a large mass of adenoids was removed; previously, there had been marked obstruction to breathing; otitis media followed

Fig. 3.—D. H. at age of 18 months.

the operation. On four occasions plastic operations were performed on the hands in an attempt to correct deformities.

Physical Examination at 18 Months of Age.—A well-nourished little girl; she holds up her head; sits unsupported; tries to stand when assisted; reaches for objects and pushes them away, but is unable to grasp them. She recognizes her father, and makes a sound interpreted by the parents as "daddy."

Her physical development may be judged from the following measurements: Weight, 9.5 kg. (average for her age, 10.6 kg.); height, 77 cm. (average, 75.6 cm.); circumference of chest, 47 cm. (average, 45.9 cm.); circumference of cranium, 44.5 cm. (average, 45.9 cm.).

The child presents no abnormalities except those of the head, hands and feet. Examination of urine and blood gives normal results. Von Pirquet test was negative; Wassermann reaction of blood was negative; cerebrospinal fluid was not obtained.

Head: The cranial vault is abnormally high; it is highest in the region of the posterior fontanel (Fig. 2). In contrast to the great height of the head is its extreme shortness and the marked breadth of face and forehead. The forehead rises almost sheer. Across it just above the superciliary ridges is a transverse groove. The portion of the forehead between this groove and the

Fig. 4.—Roof of mouth of D. H. at age of 2½ years seen from below and in ideal cross-section.

hair line bulges slightly forward. The back of the head is marked by neither curve nor prominence and is so flat that it appears to be in the same vertical plane as the neck. In cross section the cranium would approximate a square. The face is broadest in the region of the angular processes of the frontal bone and the zygomatic arches, which together form prominences causing the surface of the face to appear to be extended well beyond the eyes (Fig. 3). In consequence of the lateral prominences, the shape of the face is like that of a kite, the long diameter passing through the chin and nose. The face is unusually flat; the forehead, cheeks and chin appear to be almost in the same vertical plane. The head is symmetrical.

Both fontanels are open; the anterior admits the tip of the index finger, and is placed farther forward than normal, bordering on the edge of the forehead. The large posterior fontanel is shaped like an isosceles triangle; from its apex the sagittal suture, just perceptible, may be palpated to its junction

with the anterior fontanel; from its basal angles the lambdoidal sutures, also open, may be followed for a distance of 2 cm. When the patient was 10 months old the posterior fontanel was 7 cm. long and 4 cm. wide; a wormian bone was present, and the parietal margins were deeply serrated. At 18 months the posterior fontanel has decreased considerably in size; it now admits but the tips of two fingers. The coronal and temporoparietal sutures are closed. The site of the coronal suture is marked by a ridge. The metopic suture is open for a distance of about 3 cm. from the anterior fontanel.

Ears: The ears are large and flare outward in their upper and posterior parts. The point of junction of helix and scalp is on a lower horizontal plane than that passing through the external canthus. Hearing is acute; examination of the ear drums shows no abnormality.

Fig. 5.—Left hand of D. H. after operation for correction of syndactyly. Age 18 months.

Eyes: The eyebrows are broad and flatly arched. The eyes, rather far apart, protrude slightly. The lids approximate perfectly. The eyeballs have the appearance of being slightly rotated in such manner that their transverse axes are directed outward and slightly downward. The palpebral apertures slant in an outward and downward direction; the external canthus is considerably lower than the internal. Vision seems unimpaired. The optic disks are normal. When the child was 6 months old, ophthalmoscopic examination showed the media to be clear and the papillae unusually distinct because of the encircling choroidal pigment. A grayish tint was imparted to the disks as the result of lack of pigment in the fundus. Not only was the pigment epithelial layer of the retina wanting, as in albinos, but the intercapillary islands of stromal pigment were missing as well. Thus, the vessels were clearly visible, and the underlying capillaries and venae vorticosae of the choroid were easily traced to the most minute ramifications.[3]

Nose: The nose is thin, rather short, almost straight, and sticks out from the line of the face in a more nearly horizontal direction than normal. The ridge of the nose emerges from the line of the forehead without preliminary

3. The reports of the ophthalmoscopic findings were made by Dr. L. B. Whitham.

depression, forming with the latter an angle estimated to be about 127 degrees. As seen from in front, the lower part of the nose is extremely narrow and has a pinched appearance. The nostrils are very thin, and the apertures abnormally small.[4] The nasal septum is almost straight anteriorly but posteriorly is deflected in such manner as to cause partial obstruction on both sides.

Mouth: The mouth is small, and kept open. The upper lip is higher in its middle part than at its corners and projects forward; the open mouth forms an isosceles triangle of which the lower lip is the base. The chin is recessive. One tooth is present, a lower incisor. The hard palate is acutely arched and in cross section would appear as an inverted "V" (Fig. 4). The height of the arch measured from the level of the alveolar borders is 1.5 cm. There is malocclusion of the superior maxilla; the intermaxillary bone has not descended to the normal extent, so that the medial portion of the gums is on a higher level than the lateral. The uvula is normal.

Fig. 6.—Right foot of D. H. at age of 18 months.

Hands: The hands are essentially alike in appearance. There is a pulpy mass of flesh without definite form, which corresponds to the body of the normal hand (Fig. 5). This mass is joined to the forearm almost directly with but little intervening wrist. To the outer side of the body of the hand at its middle is attached a lump of flesh with an osseous core which bears on its dorsal tip a small nail. This lump is the "thumb." The distal portion of the hand has a pinched appearance and is composed of three operatively created "fingers," projecting like the prongs of a trident. The artificially produced cleavage extends but a short distance above the terminal phalanges. There are two phalanges for each finger and a fairly well formed nail. Before operative interference the syndactylism was almost complete; the thumb and little finger elements were, however, partially demarcated from the rest. The nails of the fingers were fused. In the operations it was found that the phalanges of the outer two digits were synostosed, and in the right hand these were divided. The bandlike nail for the fingers, likewise, was divided into three portions, one for each finger.

4. The examination of nose and throat made by Dr. S. J. Crowe.

Feet: The feet are identical in appearance (Fig. 6). They suggest normal feet over which tightly fitting stockings of skin have been drawn, leaving the nails exposed; it is possible to distinguish on palpation a tarsus and metatarsus, and two phalanges for each toe. The feet appear much shorter than the normal for 18 months.

Roentgen-Ray Examination.—Head: Roentgenograms of the head (Fig. 7) show in a striking manner as in a silhouette the abnormal outline. More effectively than the photographs the roentgenogram demonstrates the high

Fig. 7.—Roentgenogram of head of D. H., lateral view. Age 4 years 8 months.

forehead, bulging in its superior portion, the high flat occiput, and the shortened fronto-occipital and increased vertical diameters. The fontanels are open and large. There is rarefaction of all the bones of the vault especially in the occipital region. In the frontal region digital impressions indicating convolutional atrophy are especially pronounced. The site of the coronal suture cannot be determined. The deeply serrated lambdoidal suture is seen. The middle and posterior cerebral fossae are deeper than normal. The posterior and superior orbital walls join at a slightly obtuse angle. The sphenoidal angle is probably increased. On the roentgenogram made when the patient

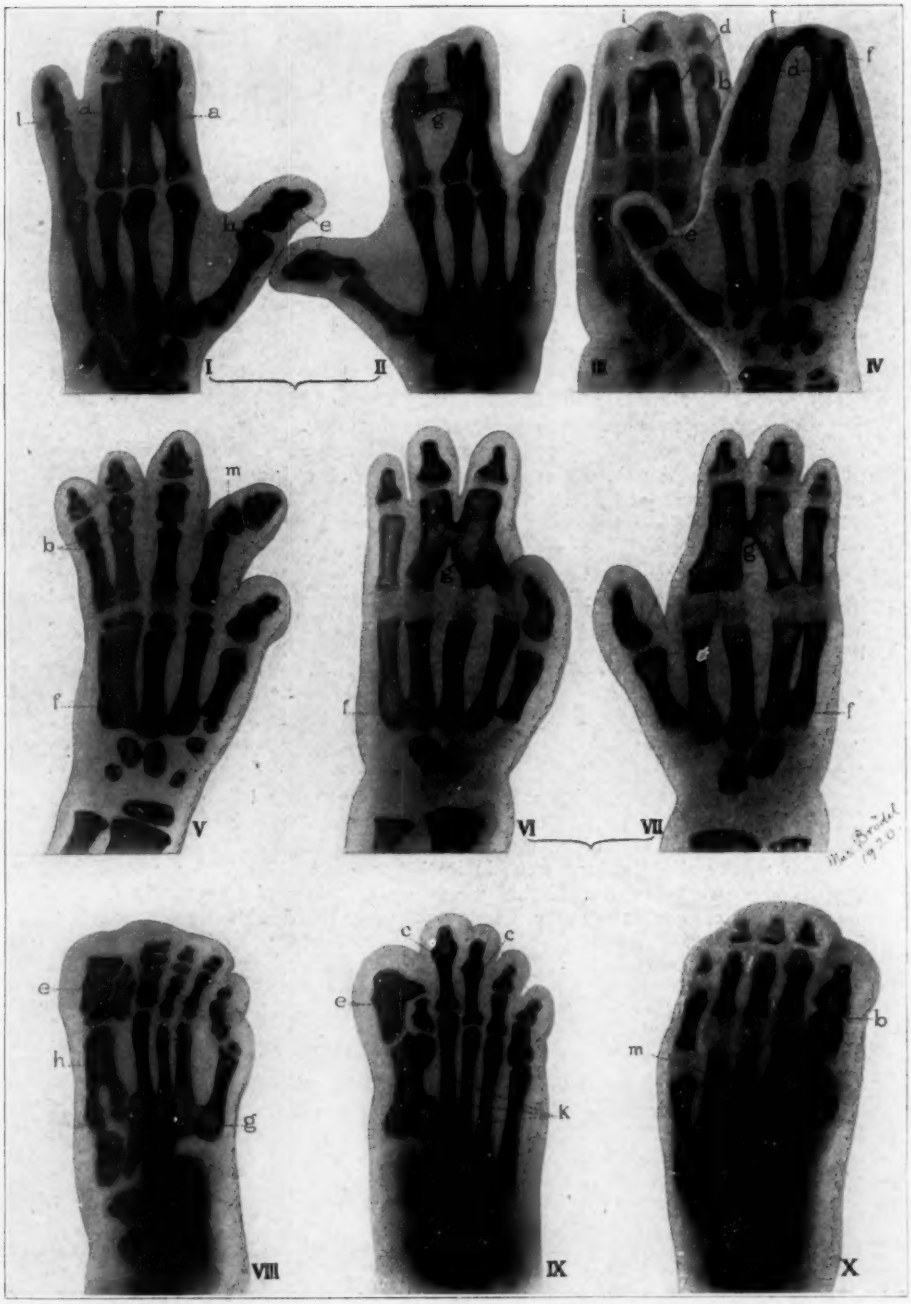

Fig. 8.—Drawings made from roentgenograms of hands and feet designed to illustrate types of malformations. Drawings I and II, Case 14, Gadelius; drawing III, Case 19, Ruh; drawing IV, Case 13, Davis; drawing V, Case 12, Bertolotti and Boidi Trotti; drawings VI and VII, authors' case; drawing VIII, Case 12, Bertolotti and Boidi Trotti; drawing IX, Case 14, Gadelius; drawing X, authors' case. For explanation of letters designating special types of deformity see text p. 264.

was 18 months old, the angle was estimated to be 160 degrees, whereas on the plate taken at 4 years 8 months of age it was considered to be 140 degrees.[5] The suture between the basi-occipital and basisphenoid bones was visible, indicating that synostosis had not taken place, and its distance from the basion was thought to be normal.

Extremities (Fig. 8, VI, VII and X, and Fig. 9).—Right Hand: There are only two ossification centers for the carpus, one for the os magnum, the other for the unciform. The five metacarpals are normal, except that the fifth and fourth seem to be united at their bases. The first and second phalanges of the ring finger are united and form a single, thick, irregularly shaped bone of about the length of the fourth metacarpal.[8] The first and second phalanges of the little finger are united and form a single bone almost as long as the metacarpal. There are three distal phalanges, one larger and longer than normal for the fused first and second phalanges of the index and middle fingers, one very large and broad distal phalanx for the ring finger, and a third, almost normal appearing phalanx, for the little finger. There is one irregular mass of bone which represents the two phalanges of the thumb. A rather broad interval exists between the distal ends of the metacarpal bones and the phalanges.

Left Hand: The bones of the left hand bear a remarkable similarity in respect to form and arrangement to those of the right. The large irregularly shaped bone representing the first and second phalanges of the index finger and middle finger, and the irregularly shaped bone representing the first and second phalanges of the ring finger, are, however, united in their middle portion.

Left Foot: The first metatarsal is abnormally large and greatly deformed. Its inner side is convex. From its outer side a bridge of bone a little less than 1 cm. in diameter runs transversely across the foot to unite with the second metatarsal. The second metatarsal approximates the normal in size and width, but is slightly bent at the point at which the bridge of bone from the first metatarsal joins it. The third metatarsal is normal, except for a distinct enlargement at the beginning of the lower third, which is not an exostosis but a general enlargement of the shaft. The fourth metatarsal presents a very slight enlargement in its lower third. The fifth metatarsal is normal. The first phalanx of the great toe is thick and irregularly shaped. The first phalanges of the other toes are probably fused with the second. The distal phalanx of the great toe is broad, pointed at the end and otherwise irregularly shaped. The terminal phalanges of the second, third, fourth and fifth toes are either normal or approximate the normal.

Right Foot: The right foot shows almost identical changes and is nearly the mirror image of the left. The bridge of bone extending from the first metatarsal to the second is not united with the latter, however, and the first and second phalanges of the big toe appear to be united.

There seems to be a general retardation in the growth of all the bones of the foot. There are no centers of ossification for the external and middle cuneiform and cuboid bones.

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5. The sphenoidal angle is the obtuse angle formed at the anterior clinoid process by lines drawn from that point to the nasion and basion. An increase in this angle is referred to as a basilar lordosis and indicates a flattening of the base of the skull.[6] The normal angle has a value according to Welcker[7] of 134 degrees. The exact measurement of this angle during life is dependent on certain conditions: (1) A roentgenogram taken with parallel rays. (2) The sagittal plane of the head must be parallel to the plate (that this condition is not fulfilled, is demonstrated by the infrequency of superimposition of homologous structures). (3) On the roentgenogram one must be able to identify accurately the most anterior point of the foramen magnum, the basion.

6. Schüller, A.: Roentgen diagnosis of diseases of the head. Authorized translation by Fred F. Stocking, with a foreword by Ernest Sachs, St. Louis. 1918, C. V. Mosby Co., p. 305.

7. Welcker, H.: Untersuchungen über Wachstum und Bau des menschlichen Schädels, I. Theil, Leipzig, 1862.

8. Prior to the operations done to correct the syndactyly this bone was united laterally to the bone representing the first and second phalanges of the index and middle fingers.

Physical Examination at 4 Years and 8 Months.—The child seems normal mentally. All the teeth are present but are crowded together. The fontanels are closed. The most striking feature is the marked bony ridge at the site of the coronal suture. The metopic suture is closed and its site is marked by a slight ridge. There is now an external squint of the right eye. Ophthalmoscopic examination revealed no fundus changes not mentioned in the previous report. Retinoscopy demonstrated a high degree of mixed astigmatism. Visual tests were quantitatively impracticable, but fair acuity of vision was present. It was impossible to demonstrate any appreciable deviation from the

Fig. 9.—Roentgenogram of feet of D. H., age 18 months.

normal relationship between the fovea centralis and the optic disk, making it impossible to prove any external rotation of the eyeball on its anteroposterior axis.

Roentgenograms made of the entire skeleton revealed no abnormalities excepting those of the head, hands and feet. Roentgenograms of the head showed the digital impressions to be more extensive and marked than at 18 months (Fig. 7).

Table 1, gives the measurements of our patient as compared with the average measurements of twenty normal children of a corresponding age.

TABLE 1.—MEASUREMENTS IN OUR CASE AS COMPARED WITH MEASUREMENTS IN TWENTY NORMAL CHILDREN

	D. H.* 18 Mos., Mm.	D. H.† 4½ Yrs., Mm.	Twenty Normal White Children, Average Age 4½ Years†		
			Average, Mm.	Maximum, Mm.	Minimum, Mm.
Greatest length of head	145	148	174.25	184	165
Greatest breadth of head	135	144	137.95	151	128
Projective ear height (tragus-vertex)	...	145	127.15	137	116
Nasion-Inion (base length)	120	139	152.95	172	138
Biauricular breadth (tragus-tragus)	110	114	113.9	123	105
Horizontal circumference of head	445	475	509.8	542	484
Sagittal arc (nasion-inion)	...	328	344.75	370	312
Transverse arc (tragus-tragus)	...	361	341.3	360	310
Smallest width of forehead	...	118	90.8	98	84
Bizygomatic breadth	120	132	112.05	121	103
Interocular breadth	30	34	27.75	32	21
External biorbital breadth	80	95	83.45	89	76
Length of ear (physiognomic)	...	57	52.70	58	47
Breadth of ear (physiognomic)	...	37	29.95	34	26
Average circumference (Horizontal Cir. + Sag. Arc + Nasion - Inion + Trans. Arc + Biauricular Breadth ÷ 3)	...	472.33	487.58	510	458.7
Cephalic index	103.8	97.3	79.18	25.1	73.9
$\frac{\text{Projected ear height} \times 100}{\text{Greatest length}}$	...	98	73	80.40	68
$\frac{\text{Ear length} \times \text{ear breadth} \times 100}{\text{Greatest length} \times \text{chin-vertex height}}$	...	7.23	4.78	5.72	3.69
Chin-vertex height	...	197			
Total face height	...	92			
Upper face height	...	55			
Nasal height	...	40			
Nasal breadth	...	24			
Breadth of mouth	...	33			
Acromion-radiale	...	179			
Radiale-stylion	...	128			
Length of hand	...	92			

* Measurements by the authors.

† Measurements by Dr. A. H. Schultz, Research Associate, Department of Embryology, Carnegie Institute of Washington. Dr. Schultz made the following comments: The anterioposterior diameter of the head of D. H. is diminished (148 mm.; normal, 165-184 mm.; average 174 mm.) but the transverse diameter is slightly greater than the average but is within the range of normal variation (144 mm.; normal, 128-151 mm.; average, 137.95 mm.). The great difference between the cephalic index (see table) of D. H. and that of normal children is, therefore, largely due to the great reduction in the anterioposterior diameter rather than to the slight increase in the transversediameter. The cephalic index, 97.3, indicates hyperbrachycephaly and is never found in normal crania. The increase in the transverse diameter is most marked in the frontal region, the width of the forehead (188 mm.) being far outside the range of normal variation for this measurement (84-98 mm.; average, 90.8 mm.). Even the orbital region is modified by this increase in the frontal width; the external biorbital breadth in D. H. is 95 mm. whereas the average is only 83.45 mm.; the interorbital breadth is 34 mm., and in normal children 27.75 mm. Increase in the frontal breadth is also found in the zygomatic region of the face. The distance between the zygomatic arches in D. H. is 122 mm. whereas the normal values for this measurement range from 103 mm. to 121 mm. Other measurements of the face show nothing abnormal except insignificant differences in the dimensions of the nose (more prominent in D. H. than in the normal children) and the mouth (breadth of mouth 33 mm., normal 37 mm.). The chief compensation for the short anteroposterior diameter is found in the greatly increased height. The projective ear height of 145 mm. in D. H. is far outside the normal variation (116-137 mm.; average, 127.15 mm.); this measurement in D. H. is 98 per cent. of the anteroposterior diameter, whereas its average value for the normal children was only 73 per cent. of the average anteroposterior diameter. The base of the skull shows great reduction in length; the nasion to inion measurement is 139 mm. in D. H., whereas it averages 152.95 mm. in normal children. On the other hand, the breadth of the base of the skull appears to be normal. (Biauricular breadth in D. H. is 114 mm.; average in normal children, 113.9 mm.) The capacity of the cranium is indicated by the average of the circumferences in the three dimensions. This is determined according to the formula: Horizontal circumference + sagittal arc + nasion-inion length + transverse arc + biauricular breadth ÷ 3. The value of this average circumference in D. H. is 472.33, whereas its average value in normal children is 487.63. Thus the cranial capacity is somewhat reduced. This would suggest that the retarded growth in length was not quite compensated for by the increase in breadth and height. The index for the relative size of the ear as determined from the formula: Ear length × ear breadth × 100 ÷ chin-vertex height × greatest length is 7.23 in D. H. but only 4.78 in normal children; this indicates an abnormally large ear.

ANALYSIS OF THE DEFORMITIES IN THE FIRST TWENTY-FIVE CASES OF ACROBRACHYCEPHALY [9]

Gadelius [10] makes the remark, "One is tempted to say of this group of patients [showing acrocephaly with symmetrical syndactylism] as of Mongolian idiots that the characteristics which mark the individual are lacking, since one abnormal person belonging to the group resembles the other." "Man vore här liksom vid mongolismen frestad att säga, at individuella särdrag saknas, det varje undermalig individ tillhörande denna form är lik den andre,"[10] page 21. As a matter of fact the finer facial characteristics and traits of expression are lost sight of in the presence of the gross defects of head and extremities so uniform and conspicuous as to confer a sort of species resemblance.

Although the descriptions in the twenty-five cases assembled suffice to establish the diagnosis, yet in a number of instances they are too incomplete and indefinite to permit of analytic study. The deficiencies in the written records are, in large part, compensated for by photographs and roentgenograms. From the combined sources of information it is possible to make the following generalizations in regard to the deformities of the head in the series of cases in question:

The head is abnormally high, short and broad. The occiput is almost flat. The eyeballs protrude and have the appearance of being obliquely set in such manner that their transverse axes are inclined outward and slightly downward. The palpebral aperture invariably has an oblique direction, so that the external canthus lies at a considerably lower level than the internal canthus.

A mere glance at the photograph of any case is sufficient to show that the vertical diameter of the head is greatly increased and that the increased height is due to an abnormal extension upwards of the cranial vault. The highest point of the head is subject to considerable variation. In the cases of Magnan and Galippe [11] (Case 3), Apert [1] (Case 10). Bertolotti and Boidi Trotti [12 b,c.] (Case 12) and Dodd and McMullen [13] (Case 21), it is stated to have been in the region of the

9. The abstracts of the twenty-four cases additional to our own will be found at the conclusion of the article.

10. Gadelius, B.: En sällsynt form af idioti med karakteristiska utvecklingsanomalier. Akrocephalosyndaktyli (Apert), Nord. med. Ark. **15**: Pt. 2, 1, 1915.

11. Magnan, and Galippe, V.: Accumulation de stigmates physiques chéz un débile: brachycéphalie, plagiocéphalie, acrocéphalie, asymétrie faciale, atrésie buccale, syndactylie des quatre extrémités, Compt. rend. Soc. de biol. **4**: Pt. 2, 277, 1892.

12. Bertolotti, M.: (a) Le syndrome oxycéphalique ou syndrome de craniosynóstose pathologique, Presse méd. **22**: 332, 1914. Bertolotti, M., and Boidi Trotti, G.: (b) L'acrocefalosindattilia di Apert considerata come una varieta fetale della cranio-sinostosi patologica, Riforma med. **31**: 679, 1915. Boidi-Trotti. G.: (c) Un caso di acrocefalosindattilia, Gior. d. r. Accad. di med. di Torino **21**: 123, 1915.

13. Dodd, H. W., and McMullen, W. H.: A case of congenital deformity of the skull associated with ocular defects, Lancet **1**: 1665, 1903.

anterior fontanel; in the case described by Davis [14] (Case 13), however, in our own case, and a number of other cases, as judged by photographs, it was in the region of the posterior fontanel. In the case of Rieping [15] (Case 20), the highest point lay between the fontanels immediately above the external auditory meatus. In none of the cases, except that of Rieping, so far as it is possible to judge from photographs, was the highest point of the head so much higher than the rest as to justify the term "oxycephaly," and in no case, unless possibly that of Ruh,[16] could the head be described as "tower" shaped.

The height of the head has not excited more comment than its shortness. As a glance at the photographs of our patient (Figs. 2 and 3) will show, the shortness of the anteroposterior diameter of the head is due chiefly to the great reduction in the prominence of the occiput. In a number of the cases the back of the head was described as flush with the neck. It is a striking fact that the surfaces of the face and back of the head are almost parallel. In Rieping's case alone (Case 20) does the occipital prominence appear to have been preserved. In Wheaton's two subjects [17] (Cases 4 and 5), aged 2 and 3 months, respectively, the length of the head was only 8.6 cm.; in Ruh's patient [16] (Case 19), aged 6 months, 11 cm.; in Bertolotti and Boidi Trotti's patient [12] (Case 12), aged 5 years, only 13 cm.; and in the first of Gadelius' series of four patients [10] (Case 14), a man aged 24 years, but 16.5 cm. In several cases the statement is made that the occipital protuberance was absent, but in one that it was unusually large.

The head relatively and actually is broad. There exists a true brachycephaly. In the ten cases in which the cranial index was recorded it ranged from 87 (Case 20, Rieping) as a minimum to 115 (Case 12, Bertolotti and Boidi Trotti) as a maximum, and in five it was 100 or more. In Ruh's and Rieping's cases the greatest transverse diameter was in the temporal region (bitemporal diameter 11.5 cm., biparietal diameter 10.5 cm. [Ruh]; bitemporal 9.5 cm., biparietal 6 cm. [Rieping]); in the other cases in which any statement was made, in the parietal region.

From the description and photographs it appears that in only one case was there asymmetry of the head. Magnan and Galippe state that in their subject (Case 3) the right frontal and the left mastoid regions were prominent, whereas the left frontal and right

14. Davis, B. F.: Acrocephalosyndactylism, Am. J. Dis. Child. **9**: 446 (March) 1915; also, J. Nerv. & Ment. Dis. **42**: 567, 1915.
15. Rieping, A.: Zur Pathogenese des Turmschädels, Deutsch. Ztschr. f. Chir. **148**: 1, 1919.
16. Ruh. H. O.: Acrocephalosyndactylism, a teratological type, Am. J. Dis. Child. **11**: 281 (Feb.) 1916.
17. Wheaton, S. W.: Two specimens of congenital cranial deformity in infants associated with fusion of the fingers and toes, Tr. Path. Soc., London **45**: 238, 1894.

mastoid regions were flattened. The right side of the forehead was higher than the left. Evidently this case was an instance of plagiocephaly as well as of acrobrachycephaly.

The circumference of the head was slightly below the normal in the cases in which record was made. Table 2 demonstrates this fact.

The face in our case was kite-shaped, as already pointed out, due to the prominence of the skull in the region of the angular processes of the frontal bone and the zygomatic arches. Davis describes the face in his case as diamond shaped, and photographs which accompany the case reports of other writers would indicate that the face was particularly wide at or above the level of the zygomatic arches.

TABLE 2.—CIRCUMFERENCE OF HEAD IN OUR SERIES OF CASES AS COMPARED TO AVERAGE FOR AGE

Case No.	Author	Age	Circumference Cm.	Average for Age* Cm.
12	Bertolotti and Boldi Trotti..	5 years	49	51
13	Davis.....	3½ years	48	48.5
14	Gadelius.....	24 years	54	55 (at 15 yrs.)
15	Gadelius.....	6 years	47	51 (at 5 yrs.)
19	Ruh.....	6 months	38	43
18	DeSalterain.....	8 years	51	52 (at 5 yrs.)
7	Ireland.....	Adult	55	55 (at 15 yrs.)
21	Dodd and McMullen	7 years	48.5	52
22	Hutchinson.....	1 year	41.8	44.7
20	Rieping.....	New born	31	35.5
	Park and Powers.....	18 months	44.5	45.9

* Data from Holt and Howland.[18]

Mention has already been made of the abnormal height and breadth of the forehead. We need add merely that in a number of the cases a horizontal groove passed across the forehead just above the superciliary ridges, and above the groove the forehead bulged forward. Indeed, a prominence of the upper part of the forehead is probably a very common feature of the deformity of the head. Specific mention of its existence was made in ten cases. In the cases in which the metopic suture had already closed, the prominence was composed of bone, but in those cases in which it was patent the prominence was due to the protrusion of the soft parts. In the case described by Maygrier [19] and Fournier [20] the prominence of the mid-portion of the forehead was thought to be a meningocele. The metopic suture was 2 cm. wide, and the adjacent margins of the frontal bone bent forward. Probably, in the majority of cases in which closure of the sutures had taken place, the bony prominence in the middle of

18. Holt, L. E., and Howland, J.: The Diseases of Infancy and Childhood, 7th Edition, New York and London, 1916, D. Appleton Co., p. 1180.

19. Maygrier: Présentation d'un enfant atteint de malformations du crâne (porencéphalie) et des extrémités (syndactylie) par hiérédo-syphilis, Bull. Soc. d'obst. de Par. 28, 1898.

20. Fournier, E.: Stigmates dystrophiques de l'hérédo-syphilis. Paris, 1898, Reuff et Cie, p. 372. [Obs. 328, p. 244.]

the forehead signified that the metopic suture had been patent, and that ossification had roofed over the protruding soft tissues. In the patient of Camus,[21] for example, aged 10½ years, the bony prominence was described as "keel shaped," and as being especially marked in its lower part. It occupied the median line of the forehead, and evidently corresponded in its position to the metopic suture. In some cases, however, the bony ridge in the situation of the metopic suture may have signified premature closure of the suture (Case 19, Ruh). The superciliary ridges have been variously described as "prominent" or "flat."

A subject of great importance in its bearing on the question of the part of the skull primarily affected is the condition of the fontanels and sutures (Table 3). Of the twenty-five subjects of the deformity, eleven were less than 18 months old. Of these six were new-born infants; the remaining five were aged 2, 5, 6, 10[22] and 12 months, respectively. In the case of the patients of Troquart[23] (Case 1) and Dubrisay[24] (Case 8), both new-born children, and very incompletely described, mention is made only in regard to the metopic suture. In Dubrisay's patient the metopic suture was no less than 2 cm. wide and in Troquart's it was patent almost to the root of the nose. It may be assumed in both instances that the anterior fontanel was open. In the case of the new-born child described by Magrier and Fournier, the anterior fontanel was 4 cm. wide, the posterior fontanel "extremely" wide. The sagittal suture became so broad between the fontanels that it formed an "accessory fontanel," shaped like a lozenge; the metopic suture was 2 cm. wide and extended from the root of the nose to the anterior fontanel. In the case of the two babies described by Wheaton, aged 2 and 3 months, respectively, a "continuous suture" ran from the posterior fontanel to the root of the nose. The metopic suture was 1¼ inches wide. The posterior fontanel must have been extremely large, for a wormian bone was present. In one of the two cases a wormian bone lay in the metopic suture also. The margins of the bones bounding fontanels and sutures were extremely irregular. In the new-born child described by Rieping the anterior fontanel was open but small, the posterior fontanel extremely large and shaped like an isoceles triangle. The base of the triangle measured 40 mm., the perpendicular 50 mm. The metopic suture was sufficiently large to contain a wormian bone 6 mm. broad and 44 mm. long. The sagittal suture was apparently partially

21. Camus, M.: Accumulation de stigmates physiques chez un dégénéré, Compt. rend. Soc. de biol. **55**:1555, 1903.

22. Our own case is included here because an examination of the patient was made at the age of 10 mos. as well as later.

23. Troquart, R.: Syndactylie et malformations diverses, Mém. et bull. Soc. de méd. et chir. de Bordeaux, 69, 1886.

24. Dubrisay, L.: Enfant atteint de porencéphalie et de syndactylie, issu d'une mere syphilitique, Bull. Soc. d'obst. de Par., 81, 1898.

closed and formed a ridge. The coronal suture was partially synostosed. The sphenofrontal suture apparently was closed. In our patient, at 10 months of age, when the first examination of the skull was made, the posterior fontanel was 7 cm. long, 4 cm. wide and contained a wormian bone. The margins of the parietal bone bordering the fontanel were deeply serrated. Even at the eighteenth month the posterior fontanel was open, and admitted the tips of two fingers. The anterior fontanel, also, was open, admitting the tip of one finger; the lambdoidal suture, still patent, could be followed for a distance of 2 cm. The metopic suture was open for a distance of 3 cm. The coronal suture was closed and probably synostosed. Its course was indicated by a well defined ridge. In the very incompletely described patient of Apert, aged 5 months, no mention of fontanels or sutures is made. It is evident, however, from the context that the anterior fontanel at least was open.[25]

TABLE 3.—CONDITION OF FONTANELS AND SUTURES IN SUBJECTS OF ACROBRACHYCEPHALY UNDER 18 MONTHS OF AGE*

Case No.	Author	Anterior Fontanel	Posterior Fontanel	Sagittal	Metopic	Coronal	Lambdoidal
1	Troquart.....	Open†	Not stated	Not stated	Open	Not stated	Not stated
4	Wheaton 1.....	Open	Open	Open	Open	Not stated	Not stated
5	Wheaton 2.....	Open	Open	Open	Open	Not stated	Not stated
6	Maygrier; Fournier.	Open	Open	Open	Open	Not stated	Not stated
8	Dubrisay.....	Open†	Not stated	Not stated	Open	Not stated	Not stated
10	Apert.....	Open	Not stated	Probably open	Probably open	Probably open	Not stated
19	Ruh.....	Open	Open	Open	Closed	Open	Open
22	Hutchinson.....	Open	Not stated	"Closed"	Open	"Closed"	Not stated
24	Cameron.....	Open†	Not stated	Not stated	Not stated	Not stated	Not stated
20	Rieping.....	Open	Open	Closed (?)	Open	Closed	Not stated
	Park and Powers....	Open	Open	Open	Open	Closed	Open

* It must be borne in mind that with the exception of the cases of Rieping and Wheaton all the data were obtained from clinical examination and in the majority of the cases were grossly incomplete.

† Condition of anterior fontanel not described. We assume, however, that, had there been so striking a departure from the normal as a closed anterior fontanel at birth, a statement to that effect would have been made.

Thus, we see that in all the subjects of the malformations less than 18 months of age at the time of examination, parts of the cranial vault were membranous, in the majority of instances to a very much greater extent than normal, and in eight cases, at least, the metopic suture was open. In Davis' patient (Case 13) the metopic suture was open at 3½ years. Only in the patient of Ruh was the metopic suture closed.

25. Apert states that "the anterior fontanel occupied the summit of the head[1] p. 1313.

In the photographs which accompany the case reports the eyes appear to be far apart. In regard to every subject of the malformations, with the exception of the three infants described by Wheaton and Rieping, seen only after death, it is specifically stated that the eyeballs were protuberant. In the patient of Magnan and Galippe, the

Fig. 10.—The patient of Ireland. Although Ireland makes no statement in regard to the elbows, the photograph suggests that the elbows were malformed in such manner that they could not be completely extended. The hands reach scarcely below the level of the pelvis and the arms are held in a partially flexed condition. Reproduced from Gadelius. (Case 7, our series.)

eyeballs protruded to such an extent that they appeared to be pedunculated and extended 1 cm. in front of the plane of the forehead. In the patient of Donaldson [26] (Case 25), the protrusion of the eyeballs was so extreme that the right eyeball had become dislocated on eleven different occasions, so that manual replacement became necessary.

26. Donaldson, E.: A Case of Deformity of the Head and Dysostosis, Tr. Ophth. Soc. U. Kingdom, Lond. **23**: 264, 1903.

In most of the more carefully described cases the statement is made that the eyeballs were set obliquely in such manner that their horizontal axes passed from within slightly downward. As already pointed out, however, in the description of our own case, it is very difficult to be certain that the eyeballs themselves were actually rotated. There is no doubt, however, that in every member of the series of whom there is photographic record, the palpebral aperture slanted outward and downward. In Ireland's patient [27] (Case 7, Fig. 10), the eyeballs were described as having divergent axes; in the first case of Gadelius' series (Case 14, Fig. 11), the right eye failed to coordinate with the left, and in his third case (Case 16, Fig 12) there was external strabismus. In our case also external squint was present.

Fig. 11.—A patient of Gadelius. The acrocephaly and brachycephaly, prominence of the eyeballs, slant of the palpebral apertures, are well shown (Case 14, reproduced from Gadelius).

The eye grounds have been examined in comparatively few cases; in our own and in Cameron's patient [28] (Case 24) they were normal. In Bertolotti and Boidi Trotti's patient optic neuritis existed; in Davis' patient the nerve head was reported as gray, the margins blurred, and some swelling present; in deSalterain's patient [29] (Fig. 13) staphyloma was present on the right side making examination of the disk impossible; on the left side the disk showed enlargement in the transverse diameter. Diminution in the acuity of vision was noted only in the patient of Bertolotti and Boidi Trotti.

The nose has been variously described as "large and thick," "flat and depressed," "the root depressed or flattened," "short and broad,"

27. Ireland, W. W.: The mental affections of children, idiocy, imbecility and insanity, London, 1898, J. A. Churchill, p. 448.

28. Cameron, H. C.: Case of achondroplasia with hydrocephalus, Proc. Roy. Soc. Med., London **12**, Sect. Dis. Child., 8, 1919.

29. deSalterain, J.: (a) A proposito de un caso de oxicefalia (Comunicacion a la Sociedad de Pediatria de Montevideo; Sesión del 15 Junio de 1917). Arch. Latinó-am. de pediat., Buenos Aires, No. 4, 1917. (b) A proposito de un caso de oxicefalia (A propos d'un cas d'oxycephalie) Sociedad de Pediatria de Montevideo, 15 juin, 1917, Rev. med. d. Uruguay **20**: 398, 1917.

"shapeless," "small and thin." In three cases it deviated to the left. From examination of photographs we should make the observation that the nose, no matter what were its lateral dimensions, was not long, and that it pointed in a more nearly horizontal direction than usual. The curious projection of the nose from the face is well illustrated in our patient (Fig. 2). The nasal apertures in our patient and in the one of Bertolotti and Boidi Trotti were extremely small. Nasal obstruction has been observed in several of the cases, and was probably present in all, due to malformations of the nasal passages, or the nasopharynx, to adenoids, or to all three.

The facies is that of chronic nasal obstruction. As shown so well in the photographs (Figs. 10, 11, 12, 13 and 14), the mouth is open; the

Fig. 12.—A patient of Gadelius. The height of the head, prominence of the eyeballs, the external strabismus, the slant of the palpebral apertures and syndactylous malformations of the hands are well shown (Case 16). Reproduced from Gadelius.

middle portion of the upper lip is elevated, and occupies a more forward position than normal. The lower lip is flat. The mouth as a whole, therefore, forms an isoceles triangle with the apex upward.

The hard palate was extremely narrow and high in all cases in which mention was made with the exception of the patient of Dubrisay and probably constitutes a constant feature of the malformation of the head (Fig. 4). In Davis' patient the palate was not only narrow and sharply arched but there was a shelflike projection along the alveolar margins. In Camus' patient the alveolar margins joined in such a way as to produce a recess in the upper part of the mouth immediately above and behind the incisor teeth. In at least five of the cases the

hard palate was cleft. It is interesting and important to note that in no instance was the cleft in the palate complete or accompanied by harelip. In the third of Gadelius' series (Case 16) the cleft in the hard palate was anterior, lying between the incisor teeth.[30] In the other cases we infer that the cleft was in the central or posterior portions. In six other cases the soft palate or uvula was bifid, and in one case, that of Régis,[31] the soft palate was said to be lacking. In twelve cases out of twenty-one, therefore, abnormalities in the formation of the hard or soft palate were noted.

Troquart stated that in his 18 months old patient dentition was normal, and Gadelius found the teeth in the first member of his series

Fig. 13.—Photographs of child with acrobrachycephaly, reproduced from De Salterain. Age 8 years.

(Case 14) in their normal situations. Certainly, in the majority of subjects beyond the age of infancy dentition was abnormal. In Bertolotti and Boidi Trotti's patient some of the incisors were behind the others.

The lower jaw presents no distinctive abnormality. In three cases it was said to be prognathic, and in two recessive.

The main features of the deformities of hands and feet can be summarized in a few words.[32] In one group the syndactylism of the

30. An undescended intermaxillary bone.
31. Régis, E.: Precis de psychiatrie. Ed. 5, Paris, 1914, O. Doin et fils, p. 1230.
32. For the exact details in regard to the deformities of hands and feet and the bizarre form and arrangement of the finger and toe nails the reader is referred to the abstracts of the case reports.

hands was complete. The fused fingers, thumb, and body of the hand formed a mass shaped like the bowl of a spoon, the concavity of the spoon corresponding to the palmar surface. The deformity in this group can be simulated by thrusting the hand into the toe of a tight stocking that crowds the ends of the fingers together. In another group all the fingers were completely syndactylous; the thumbs, however, though misshapen and functionally abnormal, were free (Fig. 12). The shape of the hand in this group resembled that of the normal hand in a tight fitting mitten. In a third group the thumbs were free and the

Fig. 14.—A patient of Gadelius. The photograph reproduced from Gradelius shows the prominence of the eyes, the slant of the palpebral apertures, the open mouth and syndactylism of hands and feet (Case 15).

little fingers partially free (Fig. 15). In a fourth group the little fingers were free for a part of their extent. The thumbs, however, were completely joined to the other fingers.

As regards the feet in the four groups of cases mentioned, either a condition of complete syndactylism existed (Fig. 6) or the great toes alone were free. Hallux varus was invariably present in all cases in which record was made (Fig. 16).

In the cases not falling into the four groups mentioned (Cases 21, 22, 23 and 24) the deformities of the hands and feet were slight but definite.

CASE 21: The phalanges of the great toes were abnormally broad; hallux varus; interphalangeal joints ankylosed.

CASE 22: Middle and ring fingers webbed; toes irregularly arranged.

CASE 23: Hands show short thumbs; only two phalanges in left index finger; toes webbed.

CASE 24: "Giant great toes and giant thumbs consisting of union of two separate toes and thumbs."

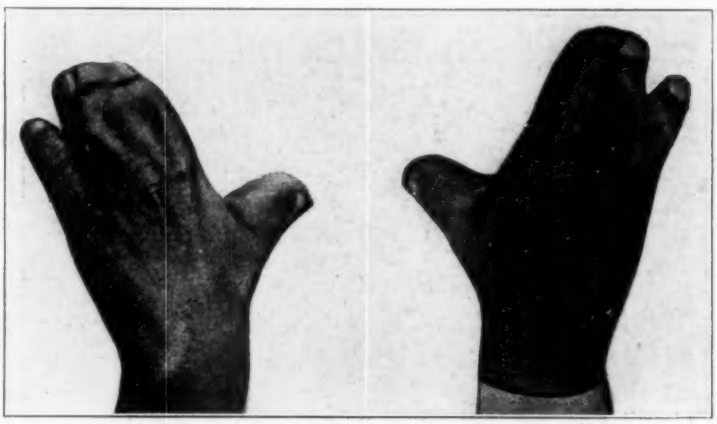

Fig. 15.—Hands of patient of Gadelius seen in Figure 12. (Reproduced from Gadelius.)

In connection with the four cases just enumerated, showing typical malformations of the head and mild degrees of malformation of the hands and feet, should be mentioned the four additional cases probably belonging to the series (Cases 25, 26, 27 and 28). The heads in all four cases were typically acrocephalic. Abnormalities in the arms and legs were noted as follows:

CASE 25: The great toes were broad and hallux varus was present.

CASE 26: "Peculiar malformation of thumbs: first phalanx curved outward toward the radial side, etc."

CASE 27: Thumbs broad, little fingers kinked, etc.

CASE 28: Elbows cannot be fully extended, etc.

Before leaving the subject of the deformities of the extremities it is most important to point out that the malformations were not limited to the hands and feet in a number of the cases. In the case of Magnan and Galippe, for example, it is stated that complete extension at the elbow joint, supination and certain other movements of the arm were impossible. In the case of Ireland the photograph (Fig. 10) shows that

the arms were greatly reduced in length, for the hands reach only to the level of the pelvis.[33] In the case of Camus, there was "synarthrosis" of humerus and radius with hypertrophy of the head of the latter. In the case of Bertolotti and Boidi Trotti there was limitation of movement at scapulohumeral articulations and at elbows (complete extension was impossible), and a synostosis between radius and ulna at the elbow was demonstrated by means of the roentgen ray. In the patient of Dodd and McMullen, the head of the radius became subluxated forward on both extension and supination of the forearm, due, in all probability, as the authors observed, to a congenital defect. In one of the patients of Fletcher[34] (Case 28) the elbows could not

Fig. 16.—Roentgenogram of feet. Patient of Régis, reproduced from Régis to illustrate symmetry of deformity and hallux varus. Age of patient about 16 years. (Case 11.)

be completely extended; the internal condyles were unduly prominent; the heads of both radius and ulna appeared to be thickened and it was impossible to raise the arms to the horizontal.

The intelligence of the majority of the subjects of the malformation appears to have been normal. In some of them, particularly in those who had found their way into institutions, the intelligence is described as subnormal. Doubtless a number of these latter became institutional inmates as the result of an inability to support themselves on account of the deformities of the extremities, or had been abandoned in early childhood for reason of their unprepossessing appearance.

Physical development appears to have progressed in almost a normal manner. Walking commenced in spite of the deformed condition of the feet at about the eighteenth month.

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33. We suspect from the appearance of the arms in the photograph that the patient was unable to extend them completely, and in consequence they appear foreshortened.

34. Fletcher, H. M.: (a) Four cases of oxycephaly, Proc. Roy. Soc. Med., Lond. **2**: Sect. Clin., 113, 1908. Fletcher, H. M.: (b) On oxycephaly, Quart. J. Med. **4**: 385, 1910.

PATHOLOGY

Head: Necropsies were done in only five cases, the two reported by Wheaton (Cases 4 and 5), that of Dubrisay (Case 8), the third of Gadelius' series (Case 16) and the case of Rieping (Case 20). For all useful purposes, however, the number of necropsies amounts only to three, since in Dubrisay's case neither head nor extremities were so much as looked at, and in the case of Gadelius, however complete the examination may have been, the report is limited to the statement that the hypophysis on microscopic examination was normal. Unfortunately, the reports of the findings in the two cases of Wheaton are too fragmentary to be of great value. The main source of knowledge is the report of Rieping.

Wheaton informs us that in both of his cases the posterior fossa was extremely narrow from before backward, and the occipital bones were extremely small. The basi-occipital bone in one case was only one-eight inch in diameter; in the other it was united to the basisphenoid by firm bony union. The bones of the cranial vault presented on their inner surfaces numerous "pits or elliptical depressions," the walls of which were extremely thin, and in some places devoid of calcium. The brain appeared to be compressed and bulged considerably when the dura mater was incised; the convolutions were flattened as if by pressure; yet no accumulation of fluid was present. The anteroposterior diameter of the brain was remarkably shortened in a manner corresponding with the shape of the cranial cavity. There was a marked lack of development of the occipital lobes, which were so small as to leave the cerebellum almost entirely uncovered. The frontal lobes also were small and pointed. No important convolutions appeared to be absent. The description of the fontanels and sutures has already been given.

The contour of the skull in Rieping's case and the condition of the sutures which were open have already been described. The coronal suture was completely synostosed for a distance of 48 mm. on each side of the skull, corresponding to the lower third and part of the middle third of each lateral half. On the inner surface of the skull the site of the synostosed suture was marked by a bony ridge 5 mm. high, continuous with the posterior border of the small wing of the sphenoid. Centering about the middle point of the synostosed portion of the coronal suture on the external surface of the skull was an area resembling a center of ossification but somewhat depressed beneath the level of the surrounding surface. The bone included in this area was considerably thickened. The patent portion of the coronal suture above the synostosis ran in an upward and forward direction instead of pursuing an upward and backward course as under normal con-

ditions. The lambdoidal suture had a more nearly vertical direction than normal. It is not perfectly clear from Rieping's description whether the sphenofrontal and sagittal sutures were partially synostosed or not. The sphenofrontal suture, at any rate, was not well defined either on the external or internal surfaces of the skull, and the sagittal suture was thrown upward into a ridge, forming a typical *crista sagittalis*. The edges of the two parietai bones forming the ridge were apparently locked together and overlapped. No parietal or frontal eminences were present.

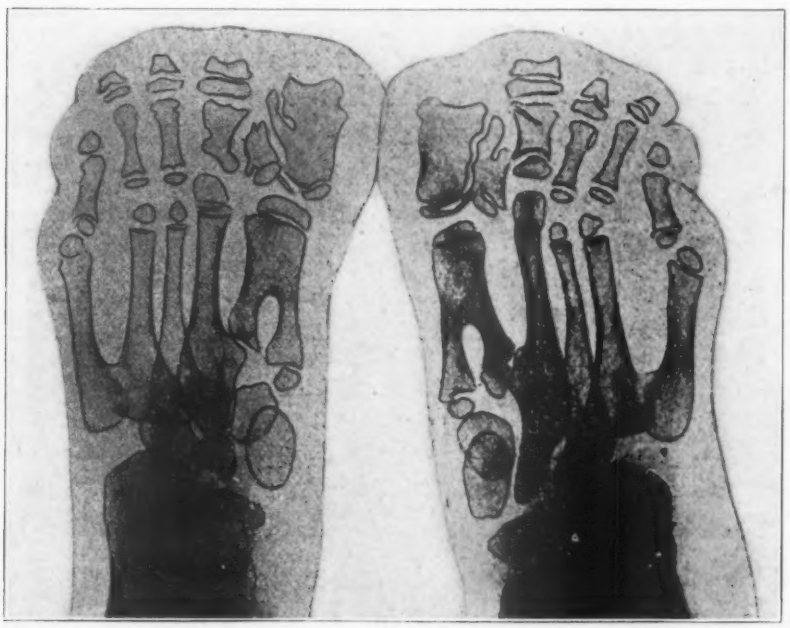

Fig. 17.—Roentgenogram of feet. Patient of Bertolotti and Boidi Trotti, reproduced from Bertolotti and Boidi Trotti to show symmetrical character of malformations. Age of patient, 5 years. (Case 12.)

The base of the skull, as viewed from above, had a rounded rather than an oval form. All three fossae were greatly shortened from before backward, and the two posterior fossae deepened. The anterior fossa was the most abnormal. The small wings of the sphenoid are described as rising upward from the body of the sphenoid like the upstretched wings of a bird. The chief part of the floor of the fossa, that which corresponds to the roof of the orbit, is said to have been more nearly vertical than normal.[35] At the same time it is described as sloping steeply downward to join the lamina cribrosa of the ethmoid. The latter was greatly depressed and lay as it were at the bottom of a

35. Rieping's description of the floor of the anterior fossa is not clear and apparently contains contradictions.

valley; it was 58 mm. below the tips of the small wings of the sphenoid as compared with 20 mm., the distance in a normal skull of a new-born child. In the middle fossa the most important feature of the deformity was the anterior position of the great wing of the sphenoid. The great wing was described as being more nearly parallel to the frontal plane than normal. The most striking features about the posterior fossa were its small size and funnel shape. Its walls sloped steeply on all sides into the foramen magnum. The pituitary fossa was larger and deeper than the fossa in the average skull. The lamina cribrosa was still in a cartilaginous condition and the sella turcica in part cartilage.

The depth of the orbital cavity was greatly reduced as a result of the downward inclination of the roof of the orbit and the forward position of the great wing of the sphenoid.

The dura, arachnoid and pia were normal.

The shape of the brain conformed to that of the cranial cavity. The cerebellum in comparison with the brain mass as a whole appeared small. An internal hydrocephalus of moderate degree was present.

Certain negative features were of moment. There was no evidence of any inflammatory condition in the membranes or bone. The optic foramen was not narrowed. There was no synostosis noted at the base. There were no digital impressions on the inner surface of the skull. The size of the sphenoidal angle was not mentioned.

The roentgenograms [36] demonstrate in a striking manner the abnormal shape of the skull, its height, breadth, shortness, the abrupt ascent and lack of curvature of the tabella of the occipital bone, the upward and slightly forward slope of the frontal. They also furnish new data. Most important, they show that there is diminution in the density of various portions of the calvarium and that digital impressions are present. In some portions of the calvarium the digital impressions appear as they actually are, that is, as circular or elliptical pits. In the frontal and occipital regions, however, where the planes of the bony walls are perpendicular or almost so to the plate, the digital impressions appear as wavy branching lines. In the case of Bertolotti and Boidi Trotti and in our case they were most numerous in the frontal region; in other cases they were found chiefly in the occipital and parietal regions.

Roentgenograms of the head also revealed that the posterior and middle cerebral fossae were not only shortened in their antero-posterior diameter but were abnormally deep. Bertolotti and Boidi Trotti state that in their case roentgenological study proved the length

36. Roentgenograms of the head are available in the reports of Davis, Bertolotti and Boidi Trotti, and Powers and Park; Ruh and de Salterain refer to roentgenograms of the head but do not exhibit them.

of the anterior cerebral fossa to be reduced and the orbital cavity to be shallower than normal. In both Bertolotti and Boidi Trotti's case and our own the roentgenograms of the head showed at the site of the spheno-occipital synchondrosis a dark bandlike shadow, proving that the synchondrosis between the basi-occipital and sphenoid bones had not yet disappeared, that is, the basi-occipital and basi-sphenoid were still ununited. They supplied evidence also of the existence of a "basilar lordosis" as shown by an increase in the size (in the obliquity) of the sphenoidal angle.

Extremities: Although no dissection of the extremities in any of the cases has been made, the roentgenograms reveal conditions in the skeletal elements with a clearness equal to that of anatomical

Fig. 18.—Photograph of embryo No. 1909 of the Carnegie Embryological Collection. Crown-rump length, 14.6 mm. Estimated menstrual age, 46 days. Outline of blastemal skeleton in hand plate clearly visible to naked eye. Development in foot plate not so advanced as in hand plate. (Courtesy of Dr. Streeter.)

preparations. We shall point out merely the principles that seem to underlie the malformations of the hands and feet (Figs. 8, 9, 16, 17).

In general it may be stated that:

(1) The maldevelopment of the hands and feet was not limited in any instance of which there are roentgenographic records to the soft parts alone but involved also the bones.

(2) The maldevelopment was more extensive in the distal portions of the extremities than in the proximal and reached its maximal development in the extreme ends.[37]

37. In one case there was limitation of movement at the scapulohumeral articulation, in seven cases at the elbow (in only two cases was there roentgenographic proof of malformation of the bones at the elbow). In all cases the bones of the hands and feet were malformed and in all cases the phalanges were more extensively malformed than the metacarpals. In all the cases with the exception of one (Case 12, Bertolotti and Boidi Trotti) the most marked malformation was to be found in the terminal phalanges of the hands.

(3) The malformation was more extensive in the upper extremity than in the lower.

(4) The malformations were bilateral.

(5) In the arrangement of the malformed parts on the two sides of the body there was exhibited a strong tendency toward symmetry. (In several cases the shadow of the intricately deformed skeleton of the hand or foot on one side was almost the mirror image of the shadow of its fellow on the other (Figs. 16 and 17). In all cases there was a correspondence in the finer details on the two sides of the body that was remarkable (Fig. 8, i and ii, vi and vii; Fig. 9).

Fig. 19.—Acrocephalic skull of new-born child, lateral view, reproduced from Zuckerkandl, showing synostosis of less than one third of coronal suture. The nonsynostosed parts of coronal suture are widely separated. Just posterior to the synostosed portion of the coronal suture, lying in the parietal bone, is an area of thickened bone with radial striations resembling a center of ossifications. Extreme degree of convolutional atrophy.

(6) The malformations consisted essentially not in new formations but in the absence or imperfect development of certain elements, namely, the structures forming the joints, the soft tissues interposed between the bones, etc., in the union of bones, and in alterations in form and size.

The malformations showed certain special features that must be pointed out. In all cases except two (Case 11, Régis; Case 14, Gadelius [Fig. 8, i *b*]), the joints between metacarpal bones and the proximal phalanges were preserved. In all cases except one (Case 12, Bertolotti and Boidi Trotti (Fig. 8, viii), so far as it is possible to determine

from the roentgenograms, the bones of the carpus and tarsus remained ununited. The integrity of the thumbs and little fingers was more often preserved than the integrity of the intervening fingers; that is, the thumbs and little fingers exhibited less tendency toward cross union, both osseous and through the intermediary of the soft parts, than the middle three fingers. In all cases there was evidence of defective development in a quantitative sense; that is, in all cases there could be found phalanges that seemed shorter than normal (Fig. 8, *l*) or thinner: than normal (Fig. 8, *k*) or phalanges were absent or cross union of phalanges or metacarpal bones with obvious reduction in substance existed (Fig. 8, *h*). In two cases (Case 12, Bertolotti and Boidi Trotti; Case 13, Davis) there was said to be evidence of reduplication of osseous elements (Fig. 8, viii). In some of the cases metacarpal bones or phalanges could be found which appeared to exceed the normal in thickness (Fig. 8, *j*). In general, if an excess of substance existed, it appeared to be in an increased thickness; if a deficiency of substance existed, it seemed to consist in a decreased length or in decreased thickness where a fusion-like union with a neighboring bone had taken place. The impression was obtained that the deficiencies in osseous substance predominated over the excess. In a number of the cases bones were abnormally shaped, even though no synostosis existed (Fig. 8, *m*).

The following types of union of metacarpal bones and phalanges could be distinguished:

1. Union of phalanges with their fellows of the same fingers.
   - (a) Union with apparently almost complete preservation of cleft corresponding to joint—possibly fibrous union (Fig. 8, *a*).
   - (b) Union of one phalanx with another with partial preservation of cleft corresponding to joint (Fig. 8, *b*).
   - (c) Complete union with formation of ridge or enlargement at site of junction (Fig. 8, *c*).
   - (d) Complete osseous union of such nature that united bones appear as one bone (Fig. 8, *d*).
   - (e) Complete union with formation of heterogeneous mass (Fig. 8, *e*).
2. Cross union between metacarpal bones and between phalanges.
   - (f) Side to side union, the outline of each bone remaining distinct—fibrous union (?) (Fig. 8, *f*).
   - (g) Partial osseous union through bridge formation (Fig. 8, *g*).
   - (h) Complete fusion with reduction of substance but retention of form (Fig. 8, *h*).
   - (i) Complete fusion into heterogeneous mass (Fig. 8, *i*).

VIEWS CONCERNING THE ETIOLOGY OF THE DEFORMITIES AND THE RELATION OF THE DEFORMITIES OF THE EXTREMITIES TO THOSE OF THE HEAD

Several authors have attributed the malformations of both head and extremities to fetal syphilis; Maygrier and Fournier because of the history of two miscarriages and the admission of a syphilitic infection on the part of the father sixteen years previous to the birth of the patient; Dubrisay on account of a history of a miscarriage and an ulceration of the genitalia, and deSalterain in spite of the absence of any history suggesting syphilitic infection and of a negative Wassermann reaction of the blood. Because of "'snuffles,' the earthy complexion, shriveled skin, fibrous thickening of the spleen" and "elliptical patches of atrophy or defective ossification of the cranial bones, and their softness during life, together with the irregular crenated edges of the bones bounding the sutures and fontanels," Wheaton expressed the opinion that the malformation of the head had been caused by fetal syphilis in both his cases.[38] Curiously enough, he regarded the malformations of the hands and feet as the effects of compression by amniotic adhesions. The amniotic adhesions, however, he thought in all probability of syphilitic origin.

Magnan and Galippe declared the malformation of the head in their case to have been caused by an inflammatory process at the base of the skull. They did not attempt to define its nature and offered no explanation for the deformities of the extremities and did not seek to bring them into causative relationship with the deformities of the head.

Although Bertolotti and Boidi Trotti referred the malformation of the head to an "abnormal disposition of the germinal layers in early embryonic life," [39] they proposed an entirely different explanation for the deformities of the extremities; according to it the deformities of the extremities were the result of maldevelopment of the skull. In order to make clear Bertolotti and Boidi Trotti's opinions concerning the relationship of the deformities of the extremities to those of the skull as well as the views expressed by other writers, it is necessary to give a brief exposition of the theory propounded in 1904 by Babes.[39a]

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38. Wheaton remarks: "I am therefore of opinion that the cranial deformity in these cases is due to fetal syphilis, although no clear history of syphilis in the parents of the infants could be obtained."[17] p. 240.

39. The views of Bertolotti and Boidi Trotti concerning the origin of the malformation of the head are not entirely clear. The inference from the above quotation is that the two authors considered the malformation of the head as germinal in origin or as acquired very early in fetal development. On the other hand, they refer to a fetal synostosis of the metopic suture occurring "in the third and fourth months of fetal life" and also of the sphenofrontoparietal sutures as if the mal-development of the skull had originated with them. In a previous publication[12a] Bertolotti very decidedly took the view that oxycephalic malformations were rachitic in origin.

39a. Babes, V.: (a) Ueber Gesichtsanomalien, welche eine Umwandlung der Extremitäten (Akrometagenese zur Folge haben), Berl. klin. Wchnschr. **41**:464, 1904. (b) Sur certaines anomalies congénitales de la tête, déterminant une transformation symétrique des quatre extrémités (acrométagenèse), Compt. rend. Acad. d. sc. **138**: 175, 1904.

In the course of examination of a series of monsters Babes observed that malformation of the extremities occurred when the base and upper parts of the facial portion of the skull were defectively developed, but not when the malformation was limited to other parts of the skull. Using Babes' own terminology, aprosopia, schistoprosopia, certain forms of cheilognathopalatoschisis, in which the base of the skull was affected, and hydrocephalus with premature ossification and sclerosis of the base of the skull were accompanied by ectodactyly, polydactyly, syndactyly, or shortening or lengthening of an extremity, single finger or toe, or by combinations of these, whereas less severe types of deformity of the skull in which the base and upper part of the face remained unaffected, were unaccompanied by malformation of the extremities. Babes concluded that there must exist in the region of the base of the skull and the facial portion of the cranium a trophic center that controlled the normal growth of the extremities. When this trophic center was absent or imperfectly developed, growth of the limb buds became abnormal. As to the location of the center Babes is not clear. He writes as if he thought it is situated in the base of the skull, but at the same time seems to permit the implication that the center may be in the hypophysis or base of the brain.

Stimulated by Babes' theory, Bertolotti and Boidi Trotti attributed the deformed condition of the extremities to a disturbed function of the hypophysis, the result of a maldevelopment consequent to the malformations of the skull. None of the authors of the case reports other than Bertolotti and Boidi Trotti seem actually to have espoused Babes' theory. Two of them, however, may be said to have flirted with it. Apert refers to it as "the most satisfactory" theory and as being "alluring and agreeing well with what the study of acromegaly has taught concerning the trophic rôle of the pituitary gland in relation to the extremities." Ruh refers to it as "one of the most attractive theories for the explanation of certain forms of atypical development."

Gadelius seeems to have lent a willing ear to the theory that a defect in the fetus' own organs of internal secretion was responsible for the malformation of both extremities and head.

Rieping considered the malformation of the head as germinal in origin. The malformation of the extremities also, he seems to have regarded as germinal. Apparently, however, he did not think that any special association existed between the malformations of head and extremities. He held that oxycephaly was a malformation especially prone to be accompanied by "other congenital malformations" and seems to have thought that the occurrence of symmetrical syndactylous deformities in his case was accidental.

To whatever extent the various authors may have differed in regard to the origin of the deformities of the skull or the relationship of the deformities of the skull and extremities to each other, all, with the single exception of Rieping,[40] seem to have agreed that the pathologic process at the base of the deformity of the skull was a premature synostosis of the cranial sutures.

Such are the facts relating to the cases exhibiting this curious combination of congenital anomalies and such the ideas expressed concerning them. We shall endeavor to show that the theories advanced in regard to etiology are untenable and shall seek to extend knowledge one step further.

SYPHILIS AS THE CAUSE OF THE MALFORMATIONS

Although there can be no doubt that malformations like those described may occur in subjects of congenital syphilis, it is scarcely necessary to bring forward arguments to prove that they are not syphilitic in origin. Fetal syphilis does not manifest itself by the production of isolated congenital malformations. While the Wassermann reaction has been furnishing repeated demonstration that congenital defects such as spina bifida, cleft palate, polydactylism, etc., are not syphilitic in origin, studies in heredity and experimental teratology have thrown light on their true sources of origin.

The symptoms and pathologic changes, almost all of them irrelevant, cited by Wheaton in favor of the existence of congenital syphilis, the meagre evidence supplied in the histories of the cases of Maygrier and Fournier, and of Dubrisay, at most suggest the possibility that congenital syphilis was present. In not one case of the entire series is there the record of any pathologic condition actually indicative of congenital syphilis, and in each case in which the Wassermann test was done (cases of Davis, Ruh, de Salterain, Powers and Park) it was negative. It is possible to exclude syphilis as the etiologic factor.

THE DEFECTIVE DEVELOPMENT OF THE EXTREMITIES NOT SECONDARY TO THE DEFECTIVE DEVELOPMENT OF THE SKULL

The theory offered by Babes rests on three hypotheses, each of which requires separate proof, (1) that the growth and development of the extremities are governed from a center; (2) that the center is situated in the base of the skull, or allowing Babes' theory the widest possible interpretation, in the contiguous portion of the brain, or in the hypophysis, and (3) that it is wanting or functionally impaired

40. Rieping's views will be discussed later (pages 283, 284).

in severe malformations involving the basal region of the skull. There can be no doubt that cleft palate in its severe forms and hydrocephalus accompanied by "premature ossification and sclerosis of the base of the skull" (Babes means cases ordinarily described as acrocephaly or oxycephaly) are much less frequently accompanied by "ectodactyly, polydactyly, syndactyly," etc., than by normal conditions of the extremities, and that, conversely, deformities of the extremities occur in by far the majority of instances in persons having normal craniums (namely, the numerous examples of familial polydactylism and syndactylism). Becase phenomena occur in combination, it in no wise follows that the relationship between them is one of cause and effect. Indeed, if their occurrence in combination is inconstant, if each happens independently of the other, the relationship between them cannot have a casual basis. We shall attempt to point out the incorrectness of Babes' theory, however, in other ways.

The fact that the growth and development of the limb buds of the embryo is not dependent on formative stimuli emanating from the central nervous system has been indicated by accidents of development and experiments. As an example of accidents of development may be mentioned the oft cited anencephalic human monster without spinal cord or motor nerves but with normal peripheral sensory nerves, muscles and skeleton, described by Leonowa.[41] The monster had a body length of 34 cm. The absence of anterior horn cells and of the anterior nerve roots was determined by microscopic examination. Other similar anencephalic amyelic monsters have been described (Herbst [42]). As a matter of fact, the discussion has raged not concerning the dependency of the osseous system for its development on the integrity of any part of the nervous system, but the dependency of the muscular system for its development on the integrity of the motor nerves. There has never been reason to assume, so far as we are aware, that the development of the skeleton was determined by nervous influences. Weber,[43] himself, has described an amyelic calf fetus with normally developed skeleton in support of the theory of a neurogenic origin for the muscular system. In the new-born calf in question the larger part of the vertebral column and the spinal cord from the level of the first thoracic vertebra was absent. Though the muscles of the hind legs were lacking, the hoofs, as well as the bones, were normally developed.[44]

41. von Leonowa, O.: Ein Fall von Anencephalie combinirt mit totaler Amyelie, Neurol. Centralbl. **12**: 218, 1893.
42. Herbst, C.: Formative Reize in der tierischen Ontogenese. Ein Beitrag zum Verständnis der tierischen Embryonalentwicklung. Leipzig, 1901, A. Georgi, p. 125.
43. Weber, E. H.: Ueber die Abhängigkeit der Entstehung der animalischen Muskeln von der der animalischen Nerven, erläutert durch eine von ihm und Eduard Weber untersuche Missbildung, Arch. f. Anat. Physiol. u. wissensch. Med., 547, 1851.
44. The joints were ankylosed apparently from disuse.

The experiments referred to, indicating that the limb buds are not dependent on nervous impulses for the assumption of normal form, are those performed by Harrison [45a, b] on frogs. Harrison removed the spinal cord in a series of frog embryos before histologic differentiation had occurred in either the muscular or nervous systems, so that the isolation from the central nervous system of the cells that were to enter into the formation of the limb buds was complete, and any formative stimuli arising from the central nervous system were eliminated. The limb buds thus freed from all nervous influences differentiated normally. Harrison transplanted the limb buds of frog larvae before the nerves of the body had grown into them, so that, when a connection with the central nervous system became established, it was an abnormal one. Yet the identity of the limb was preserved.

Although we cannot offer evidence as striking as that contained in the work of Harrison to prove that growth and development of the limb buds is not determined by any organs or combination of organs of internal secretion of the fetus, we can bring forward considerations sufficient to render any such view extremely improbable. All facts at our disposal indicate that the embryo is dependent for his proper growth and development not on his own but on the parental organs of internal secretion. Though the medical literature is full of examples of abnormal conditions attributed to disturbances in the fetal organs of internal secretion and abounds in explanations of congenital defects and disease on the basis of insufficiency in the fetus' own endocrine glands, there is not one single pathologic condition which in the present state of our knowledge can be referred to that cause with any justification whatsoever. Furthermore, clinical observation teaches that disturbances in the function of the endocrine glands may give rise to changes in the body as a whole or at least in a variety of tissues (gigantism, acromegaly, dystrophia adiposogenitalis, myxedema, hyperthyroidism, eunuchism) or to altered metabolic states such as those seen after removal of the pancreas or parathyroids, but gives no indication that they produce alterations in parts of the body which are composites of tissues, such as the head, extremities, etc., to the exclusion of other parts. It is impossible to conceive that an organ of internal secretion can cause changes to occur in the bone, muscles, connective tissue, fat and integument of certain divisions of the body and not act at all on the same tissues elsewhere.

In the single case in which the hypophysis was examined (Case 16, Gadelius) it was reported normal.

45. Harrison, R. G.: (a) An experimental study of the relation of the nervous system to the developing musculature in the embryo of the frog, Am. J. Anat. **3**:197, 1904. (b) Experiments in transplanting limbs and their bearing upon the problems of the development of nerves, J. Exper. Zool. **4**: 239, 1907. (c) Experiments on the development of the fore limb of Amblystoma, a self-differentiating equipotential system, J. Exper. Zool. **25**: 413, 1918.

The third possibility implied in Babes' theory, that a center exists in the undifferentiated tissue of the base of the skull, which presides over the growth and development of the extremities, it is not necessary to consider.

It is possible to conclude that the defective development of the extremities is independent of the defective development of the skull. From this fact it follows either that the malformations of skull and extremities have no relationship to each other or else have a common origin.

EVIDENCE OF THE EARLY ORIGIN OF THE DEFORMITIES OF THE EXTREMITIES

We might have pointed out that the deformities of the extremities dated back to an extremely early period of fetal development, before ossification had taken place anywhere, as final evidence that they could not have been caused by a defective development of the bony cranium. We now bring forward the reasons for believing that their origin was an early one but with a different object in view, namely, to shed light on the pathological condition at the basis of the cranial malformation and the period of fetal development at which it already was or became established. That the deformities of the extremities were in existence at an extremely early period of fetal development cannot be doubted after the facts relating to the normal development of the extremities are recited.

The arm bud makes its appearance about the third week of embryonic life (in an embryo 2.1 mm. long) and reaches considerable size by the fourth week.[46] In the fourth week (embryo 7 mm. long) differentiation begins to occur in the form of an increased condensation of the mesenchyme known as the skeletal core and representing the humerus, radius and ulna. The membranous radius and ulna are continuous proximally with the membranous humerus, and the membranous ulna, larger than the radius, appears to be more directly the continuation of the humerus. Distally the radius and ulna pass into an ill defined mass of mesenchyme which is the hand plate. No cartilage is yet present. By the fifth week (in an embryo 11 mm. long) the skeletal core can be differentiated into several of its elements, three of which, the humerus, radius and ulna, now contain in their central portions cartilage. By this time centers of condensation of the mesenchyme can be distinguished in the hand plate corresponding to the scaphoid, semilunar, cuneiform, trapezoid, trapezium, os magnum, and unciform bones. From these centers five cores of condensed mesen-

46. This description of the development of the arm bud is taken from that given by Lewis.[47]

47. Lewis, W. H.: The development of the arm in man, Am. J. Anat. 1: 145, 1902.

chyme radiate outward toward the end of the arm bud, but shade off distally into undifferentiated mesenchyme; they are the future metacarpal bones. At the end of the sixth week (embryo 16 mm. long) (Fig. 18) most of the skeletal elements of the arm have passed over into cartilage. The five metacarpal bones at this stage appear as slender cartilages surrounded by very thick condensed mesenchymal tissue, forming the perichondrium. The ulnar four phalanges of the first row, having passed the mesenchymal stage of development, appear as short slender cartilages deeply imbedded in condensed mesenchymal tissue. The proximal phalanx of the thumb is still composed of condensed mesenchyme. By the end of the seventh week (embryo from 18 to 20 mm. long) all the skeletal elements of the arm are cartilaginous, except the distal row of phalanges from the second to the fifth digits, which are still of condensed mesenchyme. All the muscles of the arm can now be recognized and the tendons and ligaments are well formed.

Separation of the humerus, radius and ulna and of the bones of the wrist and hand with the formation of joint cavities does not occur until the third month of fetal life.

The development of the lower extremity is identical in principle with that of the uppper extremity. Differentiation begins a little later, however, and the development does not proceed quite so rapidly (Fig. 18).

The points which we have wished to emphasize in the description just presented are these: Differentiation of metacarpal bones and phalanges involving separation from their neighbors can be seen as early as the fifth and sixth weeks of embryonic life, before they contain bone or cartilage, when they still consist of mesenchyme. At this early period of development, humerus, radius and ulna, carpal bones, metacarpal bones and phalanges, are continuous with each other, and form what might be termed a single branch or tree.

The account of the development of the arm just given furnishes strong evidence in favor of the early origin of the deformities of the extremities. Since metacarpal bones and phalanges exist separately from their fellow in the fifth and sixth weeks of embryonic life in embryos 11 mm. long, it is almost certain that the deformities of the hands, characterized by *union* of metacarpal bones and phalanges with their fellows must have been in existence at that early period.

The malformations of the skeleton of the hands and feet, as revealed by the roentgen ray, show peculiarities which seem to preclude an origin in an inflammatory process in the ordinary sense after blastemal differentiation had once taken place. It is necessary to point merely to the almost mirror image symmetry demonstrated in

the roentgenograms of the hands and feet in the patients of Bertolotti and Boidi Trotti (Fig. 17), Régis (Fig. 16) and the authors (Fig. 9); to such curious formations as the bridge of bone connnecting the middle phalanges of the index and ring finger on the hand (Fig. 8, ii g) or the island of bone lying in the concavity of the bony mass representing the two phalanges of the great toe (Fig. 8, ix) in the first case of Gadelius' series (Case 14); and, finally, to the marked hallux varus, apparently present in all cases.

In the light of the history of the development of the normal arm it seems reasonable to think, therefore, that the mesenchymal cores representing the metacarpal and metatarsal bones emerged from the solid masses of the hand and foot plates connected together at various points instead of separate and that the fingers and toes budded out united and with their skeletal cores joined together at the tips or along the sides or by means of transverse bridges, or fused. The transverse zones of less condensed mesenchyme, which mark off one phalanx from its fellow of the same finger and become the sites of subsequent joint formation, in many places did not develop at all or developed incompletely. In the case of Bertolotti and Boidi Trotti in which there was ankylosis of humerus with ulna and head of ulna with head of radius, the skeletal core representing the humerus was presumably continuous with the skeletal cores representing radius and ulna, and the skeletal cores representing radius and ulna were presumably joined together in their upper part. And, finally, in those cases in which there was limitation of motion at the elbow joint, the arrangement of the mesenchymal elements was probably such that, when at a subsequent period of development separation of humerus on the one side and radius and ulna on the other took place, it was an imperfect separation with the production of an imperfect joint like some of the imperfect joints in the fingers and toes.

ASSOCIATION OF DEFORMITIES OF SKULL AND EXTREMITIES NOT MERE COINCIDENCE

Since there is good ground for thinking that the defective development of the extremities was present at an extremely early period of fetal life, it would seem reasonable to suppose that the defective development of the skull dated from the same early period. Before any such inference can even be considered, however, it is necessary to give reasons for believing that the association of the deformities of skull and extremities was not mere coincidence, but that a relationship of some kind existed.

If the association between the deformities of the skull and extremities had been entirely accidental, it should be possible to find a variety

of congenital anomalies such as spina bifida, malformation of the heart, polydactylism, extrophy of the bladder, hydrophthalmus, etc., existing in single combination with acrocephaly, and these should occur with a frequency corresponding to the rate of incidence of each. But so far as we can determine, acrocephaly recurs repeatedly in single combination with the type of defective development of the extremities described and with other congenital anomalies, rarely, if at all.[48] Symmetrical polydactylism is said to be more frequent than symmetrical syndactylism; yet the malformation of the skull which

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48. The following case reports by Carpenter[49] relate to three children in one family, each the subject of malformations of head and extremities and also other congenital defects. We probably should have included them in our series of cases of acrobrachycephaly with defective development of the extremities. We did not do so because of the absence of an exact correspondence in the malformations of both head and extremities to those in our series. The congenital malformations in the cases in question were probably germinal in origin. The facts that a cousin of the three malformed children had malformed hands and that the malformations exhibited such fundamental similarities in all three children are the points indicative of an origin in defective germ plasm rather than of an acquired origin.

F. H.—Parents not deformed. A brother of the mother had a child with malformed hands, but without deformity of the skull. "No history of syphilis." Six pregnancies. The first two resulted in the births of the subjects of Case Reports 1 and 2, the third in the birth of a normal child, the fourth in the birth of a still-born child, said to have resembled the first two children, the fifth in the birth of a normal child, the sixth in the birth of the subject of Case 3.

Case 1.—Girl, aged 1 year, 11 months, when examined, showing deformities of the head described as follows: "Her frontal bone rose walllike, and it was on a level with the tip of her nose. Looked at from the front the forehead was pear-shaped, with the stalk of the pear at the root of the nose, and its base passed into a beak of bone. The sagittal suture passed forward for some distance in the usual direction until within a finger's breadth of the coronal suture. Here a distinct, beaklike, bony prominence . . . was encountered which ran forward for about three inches. The beak was one inch broad at its widest part, and one-half inch at its narrowest. The sagittal suture bifurcated at the commencement of this bony prominence, and on either side of it sutures could be felt. Behind the level of the coronal suture there was three-quarters inch of beaklike prominence of bone, and in front the beak merged into the base of the pear-shaped frontal protuberance of the skull. . . . The posterior and posterolateral fontanels were patent. The skull was bulged on either side above the level of the zygoma, which ended about two fingers' breadths on either side of the median beak of bone. The root of the nose was flat, the upper lids were thrust down, and also the eyes." The little and first fingers and the thumbs were partially and the ring and middle fingers completely webbed. There were six toes on each foot, all webbed completely except the little and fourth toes, where the webbing was only partial. In addition to the abnormalities mentioned, a congenital malformation of the heart apparently existed, and a hernia of the abdominal wall.

Case 2.—A girl, aged 3 years, 10 months, when examined, had a forehead somewhat like that of patient of Case 1. The forehead, however, did not overlap the tip of the nose. The skull was keel-shaped. The keel commenced at the top of the forehead and terminated above the parietal eminences. The back of the head was normal. Circumference of skull 18 inches. The eyes were prominent with heavy upper lids. The cornea was imperfectly developed, at one portion its outlines were not elliptical and the neighboring sclerotic seemed to run into the cornea. The photograph accompanying the case report indicates that the aperture of the lids was set obliquely in a downward and outward direction. The nose was short and the bridge flattened. The hands showed the same deformity as the hands of the patient of Case 1. There were six toes on each foot. The big toes and the next were partially webbed. There was incomplete webbing between the little toes and the next, and the webbing was complete in the others. An umbilical hernia was present, and a congenital malformation of the heart was thought to exist. The patient met an accidental death, aged 10.

Case 3.—A boy aged 5 weeks.[9] The skull, looked at from the front, was diamond-shaped; when viewed from the side, the forehead sloped backward in a straight line from the tip of the chin to the top of the skull. The occipital bone was thrust forward, with the result that the union of the occipital and frontal bones formed the peak of the skull. The eyes protruded frog-like, the eyeballs being kept in position merely by the lids. It was possible readily to dislocate the globes, so that they hung suspended by their muscular and nerve attachments. The circumference of the skull was 17 inches; the greatest anterior posterior 6½ inches, the greatest breadth 6½ inches; from the root of the nose to the back of the skull 5 inches. The middle and third fingers of each hand were webbed to the base of the nails. There were six toes on each foot all directed inward; the three inner on each foot were webbed. Each toe contained two phalanges, the proximal being long and evidently corresponding to the proximal and middle. There was also a hernia through the linea alba.

49. Carpenter, G.: (a) Two Sisters Showing Malformations of the Skull and Other Congenital Abnormalities, Rep. Soc. Study Dis. Child., Lond. **1**: 110, 1900. (b) Case of Acrocephaly, with Other Congenital Malformations, Proc. Roy Soc. Med., Sect. Dis. Child. **2**: 45, 1908.

characterizes our series of cases occurs with symmetrical syndactylism but not with symmetrical polydactylism.[50]

It seems most unlikely, therefore, that the association between the deformities of the head and of the extremities was merely the coincidence in one person of morbid phenomena entirely unconnected with each other. A relationship of some kind must have existed betweeen them. Either the two malformations had a common origin in defects in the germ plasm or else they were acquired together in the course of intra-uterine development from some common source.

Rieping's view, that the occurrence of syndactylous deformities of the extremities in conjunction with the malformation of the head had no special significance, was apparently formed in ignorance of the existence of the entire series of cases of the present report.

THE MALFORMATION OF THE HEAD

The malformation of the head exhibits several fundamental resemblances to the malformations of the extremities. At the same time, it shows certain differences. These differences, apparently, can be explained on the ground of the peculiar relation of the cranium to the growing brain. Because the brain is bound to fulfill its inherent demand for growth, a factor is introduced into the production of the cranial deformity, for which no counterpart exists in the case of the extremities, namely, intracranial pressure. The subject of the intracranial pressure and the rôle which it plays in the production of the cranial deformity will be discussed subsequently.

Unfortunately, the roentgen ray does not resolve the complex malformation of the skull into its parts like the deformities of the extremities. The two necropsy reports of Wheaton supply little information that cannot be supplied from other sources. The necropsy report of Rieping is the sole reliable source of information. In view of the dearth of facts, it is necessary to use indirect methods of investigation, and to apply to our cases the pathologic findings of others in kindred malformations of the skull uncomplicated by malformations of the extremities.

IS THE PART OF THE SKULL DERIVED FROM CARTILAGE THE ONE PRIMARILY AFFECTED?

The chief portions of the skull derived from cartilage are the ethmoid, the body, small wings and parts of the great wings of

50. If the data were available, with little doubt it would be possible to offer statistical proof that the relationship between the two deformities could not consist in a mere coincidence of unrelated phenomena. For example, if symmetrical syndactylous deformities of the extremities occurred once in every 1,000 births and acrocephaly once in every 1,000 births, the combination ought to occur once in every 1,000,000 births, and one case of acrocephaly with syndactylism ought to occur for every thousand cases of acrocephaly alone. It seems probable that the incidence of the deformities in combination is altogether too frequent as compared with the incidence of acrocephaly alone to permit of the possibility that the occurrence together was accidental.

the sphenoid, the basilar process of the occipital and greater part of the tabula below the superior curved line and the petrous portion of the temporal bone. These parts of the skull, with the exception of the tabula of the occipital bone, virtually form the base. Perhaps, the most important part of the base from the standpoint of the development of the skull as a whole is the axial portion. It extends from the nose to the foramen magnum, and is formed entirely of bones laid down in cartilage. It consists of the basilar process of the occipital, the body of the sphenoid and the ethmoid. *Is there evidence to show that the base of the skull, or more particularly the axial portion, is the part primarily affected?*

With the exception of Bertolotti and Boidi Trotti and Rieping, all authors who have given any opinion, have referred the primary defect to the base. The only good reason,[51] however, for thinking the primary defect basal was that Wheaton found an underdevelopment of the basilar portion of the occipital bone in one of his two cases and closure of the suture between the basilar processes of occipital and sphenoid bones in the other.

Rieping, on the contrary, proved by necropsy that the base of the skull was not defectively developed in his case. In Bertolotti and Boidi Trotti's patient roentgenograms showed the basilar portions of occipital and sphenoid bones to be ununited. In our patient also, roentgenographic study revealed that the basilar processes of sphenoid and occipital bones were still separate and comparative measurements made from roentgenograms of the skulls of normal children failed to indicate any reduction in the distance between basion and the anterior clinoid processes or in the length of the axial portion of the skull.

We may conclude that, though the base of the skull may have been primarily involved in some cases of the series, it was not directly affected in all. It is certain that the malformation of the skull could not have been limited to a defective development of its cartilaginous portions in any one of the cases.

IS THE PART OF THE SKULL DEVELOPED FROM MEMBRANE THE ONE PRIMARILY AFFECTED?

In several of the cases there was evidence of defective development of parts of the skull derived from membrane in the presence of clefts

51. The greatly increased vertical and lateral diameters and decreased anteroposterior diameter would seem to indicate an obstruction to growth in the anteroposterior diameter. The open fontanels and sagittal and metopic sutures would seem to imply that the obstruction to growth was at the base, on the ground that the vertex was free. The knowledge that the axial portion is the first part to be differentiated and the rest of the skull is formed around it as around a central shaft renders it easy to understand how defective formation of the axial portion might account for extensive alterations in all other parts. Finally, the involvement of the bones of the extremities, which are derivatives of cartilage, suggests that the base of the skull was the part affected on account of its cartilaginous origin. It must be apparent that the arguments just presented in favor of the view that the base of the skull was primarily involved are merely suggestive.

of the bony palate.[52] Camus, Magnan and Galippe, and Bertolotti and Boidi Trotti described the superior maxillary bones in their patients as actually atresic. It becomes almost certain, however, that parts of the skull formed in membrane were primarily affected in every case of our series as the result of a comparison of the deformities of the head with those in chondrodystrophy.

The peculiar form of the skull in chondrodystrophy depends on the defective development of the cartilaginous derivatives, especially those forming the axial portion, and the unrestricted development of those parts derived from membrane. If the cartilaginous portions of the skull were the only parts affected and the portions laid down in membrane remained entirely normal, the deformity of the skull ought to bear a similarity to the deformity in chondrodystrophy. This is far from being the case, however. In chondrodystrophy the occiput is especially prominent and the voluminous cranial vault bulges outward in all directions. The top of the head is evenly rounded. The fontanels occupy their normal situations and preserve their normal relations in respect to size and shape. The sutures of the vault are normal. In the malformation of the skull under consideration, on the contrary, the occiput is almost flat and the cranial vault does not bulge. The top of the head is peaked. The fontanels occupy abnormal situations and exhibit marked variations in respect to size and form. Some of the sutures of the vault are prematurely closed; others widely open. All these points of difference indicate that the defective development in our cases was not limited to the base alone. The peculiarities in the shape of the head point to a defective growth above the level of the base of one or more of the bones forming the sides of the cranial vault.

As a matter of fact, in six cases of our series there is evidence that the cranial vault was abnormal. Rieping found fusion of frontal and parietal bones and a pathological condition of the sagittal suture with the formation of a ridge. Wheaton described the "occipital portion of the skull" as defectively developed in his two cases. Bertolotti and Boidi Trotti noted a ridge at the site of the metopic suture and thought that premature closure of the coronal and sphenofrontal sutures was demonstrated by the roentgen ray. Ruh observed a ridge at the site of the metopic suture. Finally, in our case there was a ridge in the situation in which the coronal suture was thought to be and no evidence of patency was obtainable by means of the roentgen ray.

It would be necessary to be content with the most indefinite ideas concerning the pathological conditions underlying the malformations of the head in the cases under consideration, were it not for the post-mortem study of Rieping and the investigations on skulls showing

52. The superior maxilla and palatine bones are of membranous origin.

similar malformations unassociated with deformities of the extremities. The evidence derived from the several sources of information makes it almost certain that in all the cases of our series there was present a synostosis of one or more of the cranial sutures. What, then, is the underlying cause of the defective growth of the skull in cases such as ours and what is the significance of the associated premature synostosis of the cranial sutures? The subject has been under active debate for the past seventy years.[53]

THEORIES CONCERNING THE PATHOGENESIS OF MALFORMATIONS OF THE SKULL CHARACTERIZED BY FETAL SYNOSTOSIS OF SUTURES

Within the limits of this paper it is impossible to give more than a brief outline of the theories of Virchow[55] and Thoma,[56] and to mention others. The greatest amount of study has been devoted to the commonest of the cranial malformations, scaphocephaly.

The effort has been made to explain scaphocephaly and the associated synostosis of the sagittal suture on the ground of the development of a single parietal bone extending bilaterally from a medially situated center (Minchin[57] (1856), Baer,[58] Fridolin[59] (1884), instead of the usual development of the two separate bones from two separate centers. The conception of a unituberal parietal bone originated in the interesting fact that in scaphocephaly, and also in acrocephaly, there is often a thickening in the region of the obliterated suture which resembles a center of ossification (Figs. 19, 20, 21 and 22). The unituberal theory, which is applicable only to a fraction of cases, has,

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53. Backman[54] states that Hippocrates and Galen were familiar with the existence of malformations of the skull which they sought to bring into causative relationship with the condition of the sutures. General interest in the malformations of the skull dates from a publication by Virchow[55] in 1851 on malformations of the skull characterized by premature synotosis of the sutures.

54. Backman, G.: Ueber die Scaphocephalie, Anat. Hefte, Wiesb. **37**: 221, 1908.

55. Virchow, R.: Ueber den Cretinismus namentlich in Franken und über pathologische Schädelformen, Verhandl. d. phys. med. Gesellsch. in Würzb. **2**: 230, 1851. *In his:* Gesammelte Abhandlungen zur wissenschaftlichen Medizin, Frankf. a. M., 1856. Meidinger Sohn u. Comp., p. 1024.

56. Thoma, R.: (a) Synostosis suturae sagittalis cranii. Ein Beitrag zur Histomechanik des Skeletts und zur Lehre von dem interstitiellen Knochenwachstum, Virchow's Arch. f. path. Anat. **188**: 248, 1907. (b) Untersuchungen über das Schädelwachstum und seine Störungen. 1. Die Spannung der Schädelwand, Virchow's Arch. f. path. Anat. **206**: 201, 1911. (c) Anpassungslehre, Histomechanik und Histochemie, Virchow's Arch. f. path. Anat. **210**: 1, 1912. (d) Untersuchungen über das Schädelwachstum und seine Störungen. 2. Das fötale Wachstum, Virchow's Arch. f. path. Anat. **212**: 1, 1913. (e) Untersuchungen über das Schädelwachstum und seine Störungen. 3. Das postfötale Wachstum, Virchow's Arch. f. path. Anat. **219**: 80, 1915. (f) Untersuchungen über das Schädelwachstum und seine Störungen. 4. Hypostosen und Hyperostosen, Virchow's Arch. f. path. Anat. **223**: 129, 1917. (g) Untersuchungen über das Schädelwachstum seine Störungen. 5. Mechanische Wachstumsstörungen, Virchow's Arch. f. path. Anat. **224**: 78, 1917. (h) Untersuchungen über das Schädelwachstum und seine Störungen. 6. Rückblick und Schluss, Virchow's Arch. f. path. Anat. **225**: 97, 1918.

57. Minchin, H.: Contributions to Craniology, Dublin Q. J. M. Sc. **22**: 350, 1856

58. von Baer, K. E.: Die Macrocephalen im Boden der Krym und Oesterreichs, verglichen mit der Bildungs-Abweichung, welche Blumenbach Macrocephalus genannt hat, Mém. de l'Acad. imp. d. sc. de St. Petersb. **7**, serie 1860, **2**, No. 6. (Cited by Backman.)

59. Fridolin, J.: Studien über frühzeitige Schädeldifformitäten, Arch. f. path. Anat. **100**: 266, 1885.

however, been disproved and needs not be further considered. The disproof consisted in the discovery of remnants of the suture in skulls showing apparently a unituberal condition.[60]

In 1851 appeared Virchow's well known publication [55] on the deformities of the skull characterized by premature synostosis of the sutures. Although Virchow failed to distinguish between cretins and chondrodystrophiacs, and included the skulls of both in the material of his study, he set forth a classification of malformations of

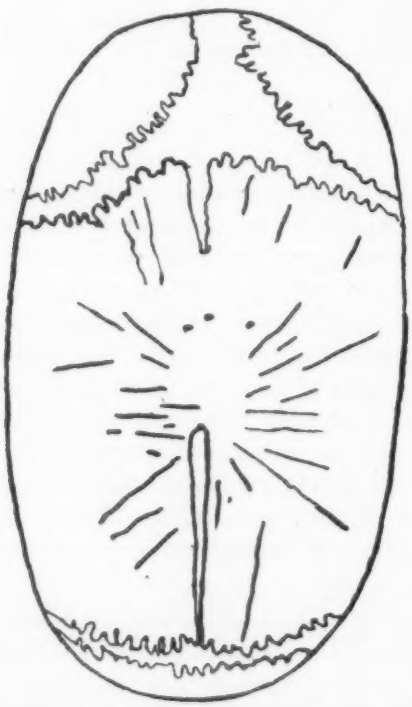

Fig. 20.—Scaphocephalic skull of fetus, reproduced from Wyman. Sagittal suture only partially obliterated. In line of obliterated suture is a thickened area of bone with radial striations resembling a center of ossification.

the skull on the basis of the relation of growth to premature synostosis of the cranial sutures which is in general acceptance today. Sömmering [61] (1839) and Hyrtl [62] (1846) had previously pointed out that an association appeared to exist between the closure of certain sutures and certain types of deformity of the skull. Virchow perceived a relationship beneath the association and defined it through

60. Wyman, J.: Observations on Crania, Museum of the Boston Society of Natural History, Boston, 1868, A. A. Kingman, p. 33. *Repr. from* Proc. Bost. Soc. Nat. His. **11**: 1868.
61. Sömmering, S. T.: Vom Baue des menschlichen Körpers, Leipzig, 1839-1845, **2**: No. 139 und 142. [Cited by Backman.]
62. Hyrtl, J.: Lehrbuch der Anatomie des Menschen, mit Rücksicht auf physiologische Begründung und praktische Anwendung, Prague, 1846, F. Ehrlich, p. 718.

the recognition of the principle that, when synostosis of two cranial bones occurs prematurely, normal growth is inhibited in a direction perpendicular to the obliterated line of suture, and compensatory growth takes place in other directions. Virchow held that the premature synostosis was the direct cause of the restriction of growth, and therefore, the primary cause of the cranial deformity itself. He seemed to have thought that an inflammatory process developed in the membranes of the brain, extended to the bones of the skull, destroyed their capacity for further marginal growth and caused them

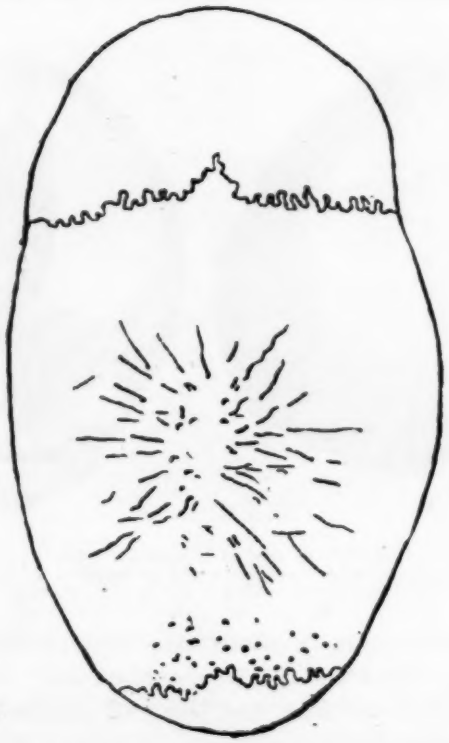

Fig. 21.—Scaphocephalic skull of 3-year-old child, reproduced from Wyman. Sagittal suture completely synostosed and not visible. In situation of sagittal suture is a thickened area of bone with radial striations resembling a center of ossification.

to become prematurely joined. The only evidence which Virchow found to substantiate the hypothesis of an inflammatory process was an eroded area, containing dilated blood vessels, in the middle part of the tabula of the occipital bone in an oxycephalic skull apparently belonging to an adult.

Virchow evidently thought that the injured skull actually obstructed the normal growth and development of the brain. He termed the condition resulting from the affection of the skull a "craniostenosis."

It would be difficult to overestimate the influence of Virchow's teachings in regard to the cranial deformities. It may be said without great exaggeration that his word has held thought bound. Though the great majority of investigators have dissented from the views expressed by him in regard to the exact mode of origin of the premature synostosis, few have challenged the basic principle involved of a restriction to growth due to a union of one bone with another before the normal time. Welcker [63] held that the pathologic process was primary in the bone. Indeed, with the exception of Broca,[64] Hirschberg [65] and a few of the earlier students of the problem, all exponents

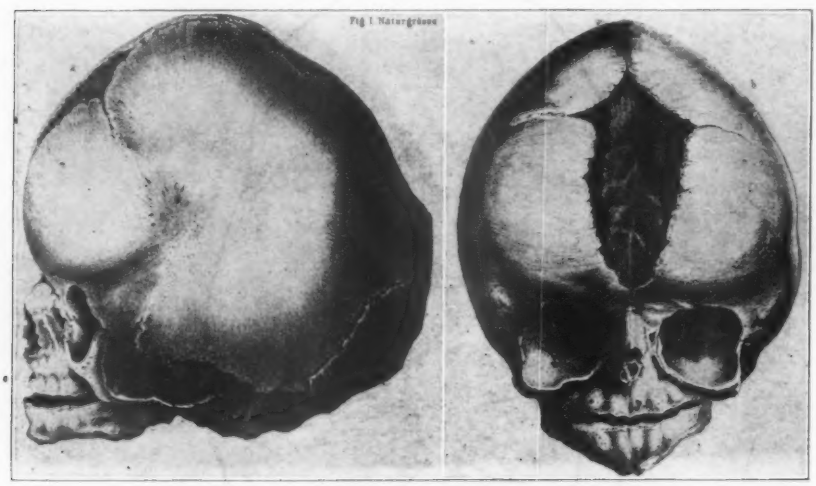

Fig. 22.—Photograph of oxycephalic skull of a new-born child, reproduced from Heschl. There is incomplete synostosis of coronal suture and in situation of synostosis an area of thickened bone with radial striations resembling a center of ossification.

of the theory of premature synostosis have looked to pathologic conditions in the bone itself for the true explanation. Bonnet,[66] Oberwarth,[67] Berkhan,[68] Vorschütz [69] and Meltzer [70] ascribed the premature

63. Welcker, H.: Ueber zwei seltenere Difformitäten des menschlichen Schädels, Scaphocephalus und Trigonocephalus, und über die Frage nach dem zwischen Hirngröse und geistiger Begabung bestehenden Wechselverhältnisse, Halle, 1863. H. W. Schmidt, p. 19. *Reprinted from* Abhandl. d. naturf. Gesellsch. zu Halle, **7**. [Cited by Backman.]

64. Broca, P. P.: Mémoires d'anthropologie, 3 v., Paris, 1871-1877, C. Reinwald & Cie, **2**: 1874. [Cited by Backman.]

65. Hirschberg, J.: (a) Sehnervenleiden bei Schädelmissbildung, Centralbl. f. prakt. Augenh. **7**: 1, 1883. Hirschberg, J., and Grunmach, E.: (b) Ueber doppelseitiges Sehnervenleiden bei Turmschädel, Berl. klin. Wchnschr. **46**: 191, 1909.

66. Bonnet, R.: Der Scaphocephalus synostoticus des Stettiner Webers, Eine Studie, Wiesbaden, 1904, J. F. Bergman.

67. Oberwarth, E.: Ueber Turmschädel, Arch. f. Kinderh. **42**: 79, 1905.

68. Berkhan, O.: Zwei Fälle von Skaphokephalie, Arch. f. Anthropol. **6**: 8, 1907.

69. Vorschütz: Zur Frage des operativen Eingriffs bei Turmcephalie, Deutsch. Ztschr. f. Chir., **99**: 386, 1909.

70. Meltzer: Zur Pathogenese der Opticusatrophie und des sogenannten Turmschädels, Neurol. Centralbl. **27**: 562, 1908.

synostoses to fetal or postfetal rickets, and Marfan [71] to rickets in some cases. Hamy [72] referred the premature synostosis to an osteitis not improbably of syphilitic origin, and Mathouillet,[73] Fournier [20] and Frasset [74] definitely regarded it as a manifestation of hereditary syphilis.

Certain investigators have expressed doubt that the theory of premature synostosis was the true explanation of the malformation of the skull, or at least that it was applicable to all cases. [Wyman,[60] Huxley,[75] Giovanardi,[76] Backman,[54] Thoma.[56]] The explanation offered by Thoma is sufficiently distinctive to justify special consideration.

According to Thoma, the closure of the sutures in the normal skull is conditioned by the interaction of three factors: (1) the tension existing in the suture substance; (2) the ripeness of the suture substance; (3) movement in the suture substance. The basic principle of Thoma's mechanistic theory of development of the cranium is that when the tension in the membrane surrounding the brain, the brain capsule, rises above a certain point, designated by Thoma the critical point, the deposition of lime salts automatically sets in, and the membrane passes over into bone. This principle he applies to the mesenchymal substance (connective tissue) occupying the sutures of the skull. When, as the result of intracranial pressure, the tension in the suture substance rises above the critical point for the tissue of which the suture substance is representative, ossification occurs and the suture closes. Ossification of the suture material takes place more readily, however, that is, at a lower critical point if the suture material is ripe (Factor 2), and is allowed to remain free from movement (Factor 3). Had Thoma defined "ripeness" as ripeness, the reader would gain almost as clear an idea of his intended meaning as from the definition actually given. "Ripeness of the suture signifies a condition in which slight changes in the determining conditions lead to its ossification." [77] In whatever alterations "ripeness" may consist, the suture material actually becomes ripe according to Thoma, if its growth ceases or diminishes.[78] The third factor of movement in the

71. Marfan: Rachitisme. *In* Traité de médicine et de therapeutique (Brouardel), Paris **3**: 1897. [Cited by Backman.]

72. Hamy, E. T.: Étude sur la genèse de la scaphocéphalic, Bull. Soc. d'anthrop de Par. **9**: 836, 1876. [Cited by Backman.]

73. Mathouillet, P. A.: Étude sur la scaphocéphalie, Paris, 1880, No. 142, p. 142. [Cited by Backman.]

74. Frassetto, F.: Appunti sulla scafocefalia patologica, Atti. d. Soc. rom. di antrop. **11**: 195, 1905. [Citd by Backman.]

75. Huxley, T. H.: On Two Widely Contrasted Forms of the Human Cranium, J. Anat. & Physiol. **1**: 60, 1867. Abstr. in Anthrop. Rev. **4**: 404, 1866.

76. Giovanardi: Di un cranio scafocefalo ed ultra dolicocefalo. Atti della società dei Naturalisti di Modena, Ser. **3**, 1894, **13**: 41. [Cietd by Backman.]

77. Thoma,[56]g page 111.

78. If, for example, growth at the sagittal suture has almost ceased, ossification of the suture substance will take place under a lower tension than if growth in the suture material were actively in progress.

suture material also requires explanation. Thoma holds that movements are communicated to the suture material of certain sutures, for example, the sagittal, coronal and lambdoidal, as the result of changes in intracranial pressure caused by the variation in arterial blood pressure with each cardiac cycle, and in the venous pressure with each respiratory cycle, and prevent closure. When the sutures do finally close, it is only because of the decline in the activity of circulatory and respiratory mechanisms with advancing age.

By means of a juggling of the three factors mentioned—at least so it seems to us—Thoma is able to explain all variations in the normal time of closure of the sutures from the closure of the metopic which takes place in the first year of life [79] to the closure of the coronal and lambdoidal sutures which take place usually during the fourth and fifth decades. By summoning a fourth factor, external pressure, he is enabled to explain all *abnormal* closures of sutures during fetal life. We are now in a position to understand Thoma's explanation of the closure of sutures prematurely in fetal life.

Premature synostosis of the sutures occurring during fetal life in scaphocephaly, acrocephaly, oxycephaly, trigonocephaly and plagiocephaly are brought about through the agency of external pressure (the new factor, Factor 4). The external pressure so alters physical and chemical conditions (tension, movement and ripeness) in the suture material that ossification is induced prematurely. The compressing mechanism is the uterine musculature. In scaphocephaly the head of the fetus is gripped by the uterus from side to side, and the margins of the parietal bones brought together and held in contact. Movement in the suture material as the result of circulatory and respiratory changes can no longer be operative. The suture material released from the tension caused by the continued pressure of the growing brain ceases to grow; therefore it becomes ripe. Although the tension in the suture substance is reduced, ossification with resulting premature synostosis takes place. It is necessary to suppose that, although the uterine wall exerts strong pressure on the sides of the head of the fetus, i. e., in the short diameter, it exerts little or no pressure on the ends, i. e., in the long diameter. Accordingly, prevented from growing in a transverse direction, the skull undergoes compensatory growth in a sagittal direction against those parts of the uterine wall in a less contracted or noncontracted state. In the case of acrocephaly or oxycephaly the premature synostosis comes about in a somewhat different way. The uterus is now conceived as gripping the head in its longest diameter, from before backwards, but as leaving the lateral

79. The metopic suture normally closes between the ninth and twelfth months according to Welcker.[68a]

portions free. The tension in either the coronal or lambdoidal sutures or in both rises; the critical point is exceeded, and ossification occurs. The factors of ripeness and movement apparently do not enter into the ossification of these sutures. In plagiocephaly (asymmetrical skull) not due to tumor or defective development of the brain, pressure is exerted by the uterine wall upon the skull diagonally, leading to an asymmetrical synostosis.

It is, of course, difficult to imagine how the uterine wall could compress the head of the fetus, as Thoma supposes, since the pressure exerted by the uterus under normal conditions is a fluid pressure. Accordingly Thoma is compelled to assume that oligohydramnios is present. Moreover, on account of the peculiar ridge formation at the sagittal suture a not infrequent accompaniment of scaphocephaly, Thoma is forced to suppose that the period at which the uterus exerts its pressure on the skull of the fetus is, comparatively speaking, late, when the margins of the flat bones are in contact with each other.[80]

Finally, it is necessary to call attention to a theory brought forward as early as 1875 by Morselli[81] and recently *de novo* by Rieping.[15] These two writers expressed the view that the premature synostosis was a physiologic process consummated prematurely because the ossification centers of the bones involved happened to be placed in abnormal proximity to each other. Morselli wrote: "If the two primary ossification points (of the parietal bones) approached each other and came to lie in the closest proximity to the *regio mediana parietalis*, this would be a very plain, simple physiological explanation of scaphocephaly in accord with the principles of histological anatomy.[82] Rieping expressed himself as follows: "The malformation (oxycephaly) is determined by variations in the germ plasm, manifested by a dislocation of the primary ossification centers of frontal and parietal bones toward the coronal suture with the result of a premature synostosis."[83]

Although the theories advanced by Virchow and his school and by Thoma appear to be widely different, in the basic principles involved they are strikingly similar. Both held that the germ plasm was normal and the fetus in all its stages of development was normal until ossification of the cranium was far advanced. Both held that the fetal cranium, including the parts immediately concerned in the premature

80. Thoma reasons as follows: If the pressure of the uterus on the sides of the head of the fetus occurred before the margins of the parietal bones had met, the sagittal suture in cross section of the skull would lie at the summit of a rounded arch. In scaphocephaly, however, the sagittal suture, if pushed upwards at all, forms the summit of a ridge (Fig. 23). Pressure must, therefore, have been exerted after the margins of the bones were in contact.

81. Morselli, E.: (a) Sullo scafocefalismo, Arch. per l'antrop., Firenze **5**: 22, 1875. [Cited by Backman.] (b) Sur la scaphocéphalie, Bull. Soc. d'anthrop de Par. **10**: 443, 1875. [Cited by Backman.]

82. Quoted by Backman,[54] pp. 234 and 235.

83. Rieping,[15] p. 44.

synostosis and defective development was normal and possessed of the normal potentialities of growth and development until suddenly deprived of them (Virchow) or of the power further to exercise them (Thoma) as the result of an accident (inflammation [Virchow], uterine pressure [Thoma]). Both held that the pathologic process at the basis of the malformation had to do with ossification.

So far as we are aware, all students of the problem, no matter what their particular views, have regarded the malformation of the skull as due to a disturbance in the process of ossification.

The theories of Virchow and his followers and of Thoma require only brief discussion. It is impossible to think that the malformation of the skull was the result of inflammation localized, so to speak, in certain of its crevices. What inflammatory process would select with such specificity a single suture line or the middle part of a suture line, or the corresponding parts of a single suture line, on opposite sides of the skull, or the same combinations of sutures, and be of sufficient severity to destroy the capacity of the cranial bones for further marginal growth and cause them to become locked together and yet disappear without leaving a trace of its existence in the synostosed bones themselves, or in the membranes beneath? Why are such inflammatory processes not found in the lines of sutures in postfetal life? There has never been produced one particle of evidence to show that premature synostosis of the cranial sutures was caused by inflammation. The theory that the malformation of the skull is the result of inflammation has, therefore, not one single fact to support it.

The reasons that the malformations of the skull cannot be caused by syphilis have already been given. The reasons that they cannot depend on rickets are only too apparent. The malformations of the skull are fully developed at birth. We have no good reason for admitting the existence of fetal rickets. Even in postfetal life there is no ground for thinking that rickets gives rise to premature synostosis of the cranial sutures. The subjects of the malformations with one or two exceptions, were apparently free from rickets.

It is also impossible to accept Thoma's theory that premature synostosis and the associated deformity of the skull are the results of pressure by the uterus on the fetus. The evidences of pressure upon the fetal skull cited by Thoma in scaphocephaly, consisting of the keel shaped ridge, the thickening of the joined parietal bones, their peculiar bend with concavity outward (Fig. 23), are not in the least convincing. How is it possible that in scaphocephaly the uterus can press together the sides of the head (the shortest diameter) and leave the ends (the longest diameter) free; and in acrocephaly that it compresses the head in the long diameter and leaves the sides free;

and that in trigonocephaly it presses together the anterior part of the head and leaves the middle and posterior parts free, and that in plagiocephaly it compresses the head in one diagonal and leaves it free to grow in the other? If sufficient amniotic fluid is present, the pressure exerted by the uterus must be fluid pressure and such gymnastic feats are impossible. If there is a condition of oligohydramnios, all parts of the fetus, not alone of the head but also of the body, should be affected. Such a question, however, as the one raised by Thoma's theory must not be decided on theoretical considerations when facts are available. Is synostosis of the cranial bones one of the recognized pathological findings in the fetus when oligohydramnios was present? We cannot find it mentioned among them. Is there

Fig. 23.—Cross-section through the synostosed sagittal suture of the scaphocephalic skull of a new-born child. The section is taken in the frontal plane at a point where union of the parietal bones is only partial. Note that the edges of the bone close to the point of union are bent upward so that externally a ridge is formed. Note also that there is a thickening of the bone on the inner side of the skull. (Reproduced from Thoma.)

a history of oligohydramnios in all cases of deformity of the skull such as we are considering? In our series of twenty-five cases a history of oligohydramnios was not given once. In three of the cases there was a history of polyhydramnios (Cases 6, 8 and 12). In our case the history stated that the amniotic fluid seemed to be abundant. Fournier[84] writes of his case: "When this woman went into labor, she discharged a quantity of fluid so abundant that it overflowed from the bed and inundated the room." One single case such as that of Fournier is enough to upset Thoma's theory.

It is difficult to accept some of Thoma's conclusions in explanation of phenomena connected with the growth and development of the *normal* skull. We cannot be persuaded, for example, that movements communicated to the suture substance as the indirect result of circulatory or respiratory activity influence the closure of the sutures or that an increase in the tension to which the suture substance is subjected, if sufficiently great, causes the suture to become prematurely synos-

84. Fournier,[20] p. 244.

tosed. In congenital internal hydrocephalus, due to an obstruction of the basal foramina or the aqueduct of Sylvius, and in acquired hydrocephalus, the result of a meningococcus meningitis, premature synostosis of the cranial sutures not only does not occur but the margins of the flat bones of the vault, though presumably still growing, actually recede from each other until the suture lines become represented by broad membranous lanes. When brain tumor develops in a child with a normal skull, the greatly increased intracranial pressure drives the cranial bones apart instead of causing them suddenly to seal together. It would be a strange provision of nature if the sudden urgent requirement for increased intracranial capacity were to be met by the withdrawal of the only means by which it could be rapidly furnished. We believe that some of Thoma's theories, when applied in explanation of the malformations of the skull of the group now under consideration, undergo a *reductio ad absurdum*.

Of all the students of the cranial deformities, Morselli and Rieping, in our opinion, have approached nearest to the most probable explanation. Rieping, in particular, entertained conceptions which, if carried to their logical conclusion, must have forced the assumption that the defective development of the bony skull was merely the expression of a defect in the blastemal cranium.

FROM THE MALDEVELOPMENT OF THE EXTREMITIES, IT IS POSSIBLE TO INFER THAT THE CRANIAL DEFECT WAS PREEXISTENT IN THE BLASTEMAL CRANIUM

If due to defects inherent in the germ plasm, the deformities of head and extremities originated synchronously, and must have emerged together out of the obscurity of the beginnings of embryonic existence. But in the event that they were acquired together as the result of some injurious influence or combination of influences after embryonic life had once been established, it is possible that the defective development of the extremities preceded that of the head. If, however, the injury to the extremities was received not later than the eighth week of embryonic life, as we believe it necessary to think if an injury was ever received at all, it is altogether improbable that the injury to the skull was delayed until ossification in the cranial vault had progressed so far that the edges of the flat bones were almost in contact with each other. From the knowledge that the deformities of the extremities almost certainly were in existence in the blastemal period, it becomes altogether likely, therefore, that the defective development of the skull was preexistent in the blastemal cranium. We believe that the facts brought out by the study of the malformations of the extremities indicate that the defective development of the

skull must be thought of as having been present in the blastemal cranium and that all theories based on the assumption that ossification was primarily at fault must be abandoned.

THE GENERAL CONSIDERATION OF THE PROCESS INVOLVED IN THE OSSIFICATION OF A SUTURE LIKEWISE INDICATES THAT THE CRANIAL DEFECT MUST HAVE BEEN PREEXISTENT IN THE BLASTEMAL CRANIUM

Ossification of membrane is to be thought of not as a formation of a new tissue but as a transformation of an existing tissue with the addition of large quantities of inorganic matter derived from the blood. Hence, the defectively developed portions of the bony cranial vault are to be regarded as the defective portions of the blastemal vault transformed from a membranous to an osseous state.

If, similarly, we inquire into the relationship of the deformities in the bony skeleton of the hands and feet to the deformities which we know must have existed in the blastemal skeleton, we come to the same conclusions. Obviously the deformities in the bony skeleton of the hands and feet can be thought of only as deformities of the blastemal skeleton transformed through the intermediary of cartilage from a state of membrane to one of bone.

If now accidental causes such as rickets, inflammation, external pressure, etc., are excluded as the controlling factors, as we believe they must be, the consideration of the process involved in the closure of a suture leads to the conclusion that the cranial defect must have preexisted in the blastema. So long as the cranial bones are separated by mesenchymal tissue through the continued transformation of which into bone they grow, they cannot meet to become synostosed. Obviously, synostosis can occur only after the separating zones of mesenchymal tissue have been completely transformed and have disappeared. Premature synostosis signifies, therefore, a disturbance not in the bone but in the growth or development of the mesenchymal matrix in which the bone was laid.

Thus, the study of the malformations of the hands and feet and general consideration of the process involved in the synostosis of the cranial sutures alike indicate that the malformation of the skull, in a potential sense, at least, was already in existence in the blastemal cranium. Either the defect must have arisen in the mesenchymal capsule or its precursors or have been present in the germ plasm itself.

THE PROBABLE MEANING OF SYNOSTOSIS OF THE BONES OF THE CRANIAL VAULT IN FETAL LIFE

From the situations of the lesions along the lines of suture in the malformed skulls under consideration, it is possible to infer that the

defective portions of the blastemal vault could not have corresponded in their arrangement to the pattern later established in the bony vault through the formation of the cranial bones, but that they must have lain in places destined under normal conditions to include the sites of sutures; i. e., the defective portions appear not to have corresponded to the individual primordia [85] of cranial bones.

The general principle involved in premature synostosis must be as follows: The margins of two islands of bone extending toward each other in the blastemal matrix meet prematurely and unite for the reason that the mesenchymal tissue between them does not keep them apart. Under normal conditions the mesenchymal tissue intervening between the margins of two bones keeps the bones apart, or at least delays their progress toward each other by continuous interstitial growth. It is easy to understand that, if the mesenchymal tissue did not grow at all, or grew at a diminished rate, the margins of the bones would prematurely come in contact with each other. If, now, the essential element in the defect in the blastemal cranial vault consisted in the loss of, or diminution in, the property of normal growth, premature synostosis might be conceived of as occurring for the reason that growth of the blastema ceased prematurely. It would, then, be necessary to think that all the steps requiring years for completion in the closure of a suture in the normal cranium followed close on each other in the defectively developed cranium of the fetus, and were condensed, so to speak, into a period of a few days or weeks.

There is reason to think, however, that synostosis of the cranial bones reaching completion in fetal life is more than a simple acceleration of the normal process. Just as the structures which comprise the joint, the articular cartilages, ligaments, etc., resist ossification indefinitely, so, as is well known, the residuum of the blastemal membrane that comes finally to occupy the lines of suture between the cranial bones, namely, the suture substance, resists ossification in some of the suture lines for years after growth has ceased. It is possible that in the malformed crania blastemal tissue, perhaps, in particular the blastema corresponding to the ultimate suture substance, possessing very probably special properties of growth and resistance to ossification, was defectively developed or actually absent? Such a possibility is suggested when the analysis of the development of the pathological synostoses in the deformed extremities is attempted.

If inquiry is made into the cause of the end to end synostosis between the phalanges, to take a specific example, the first and second phalanges of the left great toe in our case (Fig. 9), the explanation in

85. By primordium of a cranial bone is meant that portion of the blastemal cranium which ultimately becomes transformed into a cranial bone.

principle appears to be as follows: From the fact that the bones of the extremities are preformed in cartilage it seems necessary to suppose that at an early period of embryonic life the cartilaginous first phalanx and the cartilaginous second phalanx were in contact with each other instead of being separated as under normal conditions by mesenchymal elements representing the structures forming the joint. As ossification progressed in the two cartilaginous phalanges in question and the margins of the growing cores of bone moved toward each other, they inevitably met and synostosis took place for the reason that the cartilaginous matrices predestined to become bone were in contact, that is, because no nonosteogenic tissue existed between the two cartilaginous phalanges that could keep them separate. If, now, inquiry is made into the cause of the side to side synostosis accompanied by bridge formation between the metacarpal bones of the right great and second toes of our case (Fig. 9), the explanation must be the same as that already given. It is necessary to think that in fetal life the cartilaginous metacarpal bones representing the two osseous metacarpal bones were connected by a cartilaginous bridge. As the margins of the central cores of bone approached across the bridge, they met and fused because cartilaginous matrix predestined to become bone was continuous with cartilaginous matrix predestined to become bone; in other words, they met and fused because the nonosteogenic tissue normally interposed between them was absent.

The study of the pathologic synostoses of the extremities suggests, therefore, that in the blastemal cranial vault blastemal elements were actually lacking or in some way defectively constituted with the result that when ossification began, the primordium of one cranial bone was in immediate contact or continuous with the primordium of another. Naturally, it is not possible to arrive at positive conclusions concerning the causes which led to the pathologic closure of the sutures in fetal life. It seems to us necessary to infer, however, that blastema was lacking, or defectively constituted, in the sense that it never grew or grew imperfectly or did not develop the qualities enabling it to resist ossification.

In regard to the *ultimate* nature of the defect in the blastemal cranium, there is nothing to say. In all congenital malformations the ultimate nature of the defect is enveloped in impenetrable obscurity. In congenital esophageal stenosis, for example, we know that a portion of the alimentary tube remains in a rudimentary state, and in congenital pulmonary stenosis that the infundibulum or the valvular orifice does not develop. We cannot even surmise what substance or inherent force was lacking in the tissues themselves or what inhibiting influence was exerted which prevented natural conditions

from being realized. Until the forces and principles which determine normal growth and the assumption of normal form are understood, it is idle even to speculate concerning the abnormal.

CERTAIN POINTS OF SIMILARITY IN THE MALFORMATIONS OF HEAD AND EXTREMITIES

It is impossible not to be impressed by certain similarities between the malformations of the extremities and those of the head in our cases.

1. The malformations of head and extremities are both regional defects involving soft tissues as well as bone.

2. In both skull and the skeleton of the hands and feet the striking lesion is synostosis, pathologic in the case of the extremities, because it ought never to have occurred, pathologic in the case of the skull, because of its occurrence before its time.

3. In both skull and extremities those parts developed last (the vault of the skull, the ends of the extremities) appear to be most affected.

4. In the distribution of the deformities in the skull and extremities there is exhibited a common tendency toward symmetry.

If the skulls in the twenty-five cases were available for study, we believe that we should be able to find counterparts for various types of deformity in the bones of the extremities, such as union of two bones for only a part of their length, union for their entire length, union partial or complete with essentially no reduction in the width of the bones involved, union partial or complete with moderate or marked reduction in the width of the affected bones, defects of very limited extent associated with extremely slight malformations in the shape of the skull, defects so widespread as to include most parts of the osseous cranium. As a matter of fact, we already know of the existence of skulls exhibiting types of malformation similar to types of malformation present in the hands and feet. The scaphocephalic skull of a 3-year-old child described by Wyman [60] (Fig. 21) shows a synostosis of the two parietal bones so complete that the two bones appear as one. A fetal scaphocephalic skull described by the same author (Fig. 20) is characterized by union of the two parietal bones only in their middle part. The oxycephalic skull of a new-born child described by Heschl [85] *a* (Fig. 22) is marked by an almost complete fusion of frontal and parietal bones. The acrocephalic skull of a new-born child described by Zuckerhandl [86] (Fig. 19) displays central union

85*a*. Heschl: Fötale und prämature Obliterationen der Schädelnähte nach Fällen der Grazer Sammlung, Vrtljschr. f. d. prakt. Heilk., Prag. **123**: 1, 1874.

86. Zuckerkandl, E.: Ueber oxycephale und acrocephale Cranien, Mitth. d. anthrop Gesellsch. in Wien **4**: 153, 1874.

of frontal and parietal bones of slight extent with gaping sutures on either side comparable, perhaps, to union with bridge formation seen in the extremities. The greatly malformed acrocephalic skull of Fridolin [59] (Fig. 24) is an example of multiple synostosis.

THE BLASTEMAL CRANIUM NOT TO BE REGARDED AS A SHEET OF INDIFFERENT CONNECTIVE TISSUE

According to our conception of the origin of the malformations of the bony cranium, it is difficult to regard the blastemal cranium as a sheet of indifferent connective tissue, having no individuality and chancing to undergo ossification merely because it happened to be so

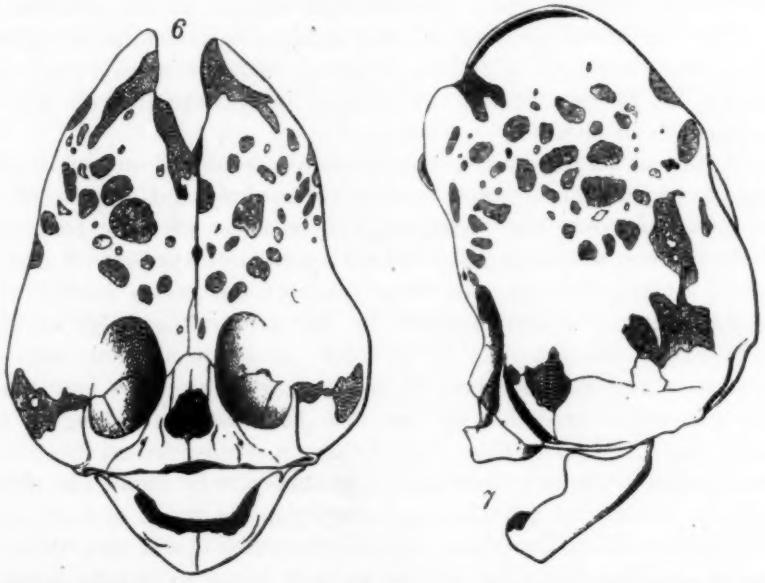

Fig. 24.—Acrobrachycephalic skull of a new-born child, front and lateral views, reproduced from Fridolin. Coronal suture synostosed, except in its upper part. Lambdoidal suture synostosed except perhaps in its lower part. Extreme degree of convolutional atrophy.

situated as to become subject to the peculiar pressure influences of the growing brain. It seems to us reasonable to think of the blastemal cranium as possessed of the same specialization as the blastema of the hand and foot plates or the blastemal precursors of all other parts of the skeleton. It seems probable that, as growth proceeds, there develops in the blastemal cranium a blastemal skeleton corresponding to the future osseous skeleton, exactly as a blastemal skeleton corresponding to the future osseous skeleton is formed in the hand and foot plates. In the extremities the various bones are separate from each other. Their blastemal representatives are distinct and permit of recognition, even though the distinction from the environment con-

sists solely in an increased density. In the cranial vault conditions are totally different. The skeleton there forms a continuous surface and the recognition of a blastemal skeleton, differentiated merely by a condensation of mesenchyme, is rendered extremely difficult. As we have already indicated, the development of the membranous cranium has never been adequately studied and still remains in obscurity.

EVIDENCE OF INTRACRANIAL PRESSURE IN EXCESS OF THE NORMAL

We now turn to the consideration of the intracranial pressure. There is evidence that the intracranial pressure has exceeded the normal in the great majority of subjects of the malformations of the skull under consideration. The evidence consists in the presence on the inner surface of the skull of areas of atrophy as determined during life by the roentgen ray and by direct examination at necropsy, and, further, in the development of changes in the eye-grounds and of disturbances in vision.

So far as we are aware, convolutional atrophy is an almost constant accompaniment of well marked acrocephaly and scaphocephaly. We have seen only one roentgenogram in either of those conditions in which convolutional atrophy did not appear to be present; it may be a most striking feature. In those cases of our series studied with the roentgen ray it was present. So far as our knowledge extends, convolutional atrophy has been noted in all necropsied cases of oxycephaly and scaphocephaly, in which search for it has been made, with the single exception of one case happening to belong to our series, that of Rieping (Case 20). Wheaton commented on its striking development in the two cases studied postmortem by him. The almost constant presence of convolutional atrophy in the group of malformed skulls under discussion proves beyond reasonable doubt that an intracranial pressure in excess of the normal is an extremely common associated condition.

The alterations in the eye-grounds and the visual disturbances, present probably in a majority of cases, can be explained only on the ground of an increased intracranial pressure.

THE CAUSE OF THE INCREASED INTRACRANIAL PRESSURE

There are three possible causes for the increased intracranial pressure: Either the cranium is abnormal and offers an increased resistance to normal growth of the brain or the intracranial contents are abnormal and generate an increased intracranial pressure or both conditions are present. We shall first consider the possibility that the increased intracranial pressure is the result of a craniostenosis, the cranial contents being normal.

According to the views already expressed, certain parts of the cranium are defectively developed. It is presumable that these parts do not furnish their normal quota of surface per unit of time in response to the pressure demands of the growing brain. If the growth of the brain continues uninterrupted, it is necessary that portions of the cranium, capable of response, contribute more than their normal quota of surface per unit of time. To make such portions grow faster than at their normal rate or possibly in excess of their normal limits increased pressure is required. Intracranial pressure, therefore, rises.

The explanation for the development of the increased intracranial pressure just given is hypothetical. Provided, however, an internal hydrocephalus is not the cause, in principle it must be assumed to be correct, whether the theory of origin for the defective development of the cranium offered by us or the theories of Virchow, Morselli or Thoma are accepted. It is probably tenable, if (1) the expansive growth of the cranium varies directly with the intracranial pressure and (2) the brain substance will generate an intracranial pressure in excess of the normal in order to fulfill its inherent demand for growth.

Observations made in the study of internal hydrocephalus and microcephalus make it appear that the expansive growth of the cranium bears a relationship to intracranial pressure. So far as we know, the cranium never undergoes expansive growth independently of the growth of its contents. We can supply no direct evidence, however, to show that the brain can create an intracranial pressure above normal limits except the very inconclusive observations of Wheaton and those of Schumacher.[87] Wheaton noted at necropsy in his two cases that the brain seemed to be under increased tension from the manner in which it bulged through the dura mater as soon as the latter was incised. At necropsy in a subject of oxycephaly showing during life indubitable evidences of an increased intracranial pressure, Schumacher failed to find evidences of a hydrocephalus. The conclusion follows that the brain tissue had generated the increased pressure in order to accomplish its growth against an increased resistance. There is little doubt that in common with other tissues the brain has the power to create a pressure in excess of the normal when its growth is obstructed, though it undoubtedly possesses this power to a much more limited extent than the less highly specialized tissues.

The second of the three possible causes for the increased intracranial pressure is "internal hydrocephalus." That internal hydrocephalus gives rise to increased intracranial pressure is too well known to require discussion. The question to be considered is whether in the malformed skulls an internal hydrocephalus is present. As just pointed

87. Schumacher, E. D.: Entlastungstrepanation oder Balkenstich bei Turmschädel mit Hirndruckerscheinungen? München. med. Wchnschr. **59**: 2282, 1912.

out, in Wheaton's two cases an internal hydrocephalus was not present. Strongly suggestive of the nonexistence of hydrocephalus in the series of cases collected by us is the fact that in those subjects measured the circumference of the head was less than the normal (Table 2). In Rieping's case, however, a small internal hydrocephalus was discovered at necropsy, even though the circumference of the head was under the normal figure. In a number of the subjects of oxycephaly and scaphocephaly unaccompanied by malformation of the extremities, the existence of internal hydrocephalus has been proven at necropsy. In the case of a scaphocephalic patient under our observation an internal hydrocephalus apparently of considerable proportions was demonstrated during life (Case 30). On the other hand, uncomplicated cases of scaphocephaly have been reported in which no internal hydrocephalus was demonstrable at necropsy.

The data at hand are altogether too insufficient to permit of positive conclusions. It appears, however, that in some cases of well marked acrocephaly and scaphocephaly no internal hydrocephalus is present. It is certain that in other cases an internal hydrocephalus of considerable proportions is present. If hydrocephalus was present in our series, it did not reach well marked degrees of development in any of those cases in which measurements of the skull were taken and probably in none of the cases.

The reason that internal hydrocephalus should be associated with synostotic malformations of the skull, except as a chance occurrence, is not clear. The possibility that the internal hydrocephalus is merely the result of a disturbed relation between the formation and absorption of the cerebrospinal fluid secondary to the craniostenosis apparently cannot be entertained. According to the explanation offered by Rieping, the internal hydrocephalus is the result of an interference in the circulation of the cerebrospinal fluid, due to a narrowing of the passageways because of the cramped condition of the brain. Another possible explanation is that the membranes themselves are defectively developed. The membranes surrounding the brain are most closely related to the skull in origin and development. It would be easy to understand that the membranes might share in the defect. We cannot offer any explanation for the coexistence of internal hydrocephalus and the cranial malformation that is satisfactory.

We are inclined to believe that the defective development of the cranium can be the sole cause of an increased intracranial pressure. In those cases, however, in which hydrocephalus is present, it cannot be denied that it may be a factor. In some cases it is probably the chief factor concerned.

We are under the impression that the intracranial pressure in the great majority of cases of acrocephaly and scaphocephaly does not reach extreme degrees of development. We have seen a case of acrocephaly and one of scaphocephaly complicated by small meningoceles. In the one the meningocele appeared only when the child cried; in the other it was constantly present but was not under tension.

ELEMENTS IN THE CRANIAL MALFORMATION APPARENTLY ATTRIBUTABLE TO THE INCREASED INTRACRANIAL PRESSURE

According to our conceptions, even if there had been no force in excess of the normal within the cranium, it still would be necessary to suppose that the skull, as a whole, would not have been normally formed on account of the defective development of certain of its parts. Under the influence of an increased intracranial pressure it would seem that the disproportionate development must have been greatly augmented. Apparently parts of the cranium capable of response to the stimulus were forced to grow beyond the normal limits in whatever directions growth could take place most easily; no part of the skull, however remote from the intracranial cavity, entirely escaped the deforming effects and the relations of all parts of the skull to each other, especially those forming the cerebral cranium, were profoundly disturbed.

The malformation of the cranium is exceedingly complicated. We cannot attempt to analyze it but merely mention some of the striking elements for which the increased intracranial pressure appears to be responsible. The excessive height and breadth of the cranial vault, the low level of the lamina cribrosa and the great depth of the middle and posterior fossae must be regarded as the effects of an increased pressure. It is probable that the flattening of the base, i. e., the reduction in the acuity of the sphenoidal angle, when present, is an expression of the effect of the increased pressure, as Bertolotti and Boidi Trotti considered. The malformation of the orbit is attributable, at least in part, to the increased pressure. The necropsy study in the case of Rieping and similar studies in cases of oxycephaly uncomplicated by malformation of the extremities have shown that the depth of the orbit is reduced. We have seen a similar reduction in the depth of the orbit in the artificially deformed skull of a Flathead Indian. The eyeball is more prominent than normal merely because the orbital cavity is more shallow than normal. The slant of the palpebral aperture and the external rotation of the eyeball about its anteroposterior axis are to be explained in all probability by an alteration in the lateral contour of the orbital cavity of such nature that its outer part

has come to occupy a lower level than its inner and the transverse diameter has acquired a direction from within outward and downward. In the normal infant, the transverse axis of the orbit is directed only slightly downward. In the greatly malformed acrocephalic skull of a new-born child described by Zuckerkandl (the skull shown in Fig. 19 but in anteroposterior view) the transverse diameter of the orbit is directed outward and considerably downward and in the still more malformed skull of Fridolin the transverse diameter of the orbit (Fig. 24) has become almost vertical. The external strabismus which developed gradually in our case and was a feature in a number of other cases is probably also to be explained on the ground of the malformation of the orbital cavity. The great breadth of some of the lines of suture and the large size of the anterior or posterior fontanels are probably to be interpreted as in ordinary internal hydrocephalus on the principle that growth in the membrane separating the bones has occurred under the stimulus of the increased intracranial pressure with such rapidity that the margins remain widely separated. The reason that the posterior fontanel was larger than the anterior fontanel in our case and the case of Rieping probably was that the expansive growth occurred there more easily than in the region of the anterior fontanel.

We cannot explain the presence of the large serrations along the edges of bone bordering on gaping fontanels and sutures, noted in the case of Wheaton and in other cases, and the presence of the wormian bones in the large fontanels and sutures. We are able to point out merely that wormian bones and marked irregularities in the edges of the bones are frequently met with in the subjects of ordinary internal hydrocephalus with large fontanels and widely patent sutures. They have no specific significance in the malformations under discussion.

THE SIGNIFICANCE OF THE PRESENCE OF A MASS OF BONE RESEMBLING A TUBEROSITY AT THE POINT OF SYNOSTOSIS AND THE APPARENT ABSENCE OF THE TUBEROSITIES FROM THEIR NORMAL SITUATIONS

In a study of 116 cases of scaphocephaly, the majority taken from the literature, Backman reported that the parietal eminences were absent in sixty-seven. In the remaining forty-nine cases they were present. In thirty of the forty-nine cases the eminences were rather poorly developed but in the remaining nineteen they were well developed. Backman's observation that in those cases in which the scaphocephalic deformity was extremely marked the parietal eminences were in general wanting may have special significance.

Why should the parietal and frontal eminences ever appear to be absent in malformations of the skull accompanied by intra-uterine synostosis of the sagittal, coronal or metopic sutures, and a circular thick mass of bone with peripheral radiations, bearing some resemblance to a parietal or frontal eminence, mark their junction (Figs. 19, 20, 21, 22). We cannot answer the question, but suggest two hypotheses.

The first hypothesis is that the circular mass of bone resembling a center of ossification is not actually a center but represents a defective area in the blastemal vault. It is conceivable that the defect in the blastema might manifest itself in the bony vault by an increased thickness as well as by a diminished growth in surface dimensions. *A priori* various irregularities in ossification in the region corresponding to the blastemal defect might be expected. The second hypothesis is that the blastema separating the centers of ossification or, perhaps, including one of them, was lacking or did not develop normally, with the result that the two centers merged or only one developed. This hypothesis falls into agreement with the observation that in marked synostotic malformations of the skull the tuberosities often appear to be absent and would make comprehensible their proximity to each other when present. It differs fundamentally from the explanation offered for the same phenomenon by Morselli and Rieping. Rieping assumed that the conditions and processes in operation in the oxycephalic cranium were normal, except that the centers of ossification, through an oversight of nature, happened to be placed in abnormal proximity to each other. He seems to have thought that as soon as the margins of the bones of the vault met, synostosis occurred and consequently that the time of occurrence of synostosis of one cranial bone with another was determined merely by the distances that separated their respective centers of ossification and to have been oblivious to the fact that along certain sutures the edges of the cranial bones lie in virtual contact with each other for twenty, thirty or even forty years before synostosis takes place. No matter how close to each other in the membranous cranium the centers of ossification happen to be placed, it would by no means follow that synostosis would occur prematurely and the centers become one.

RIDGE FORMATION AT THE SITE OF THE SYNOSTOSED SUTURE

The study of the hands and feet furnishes evidence that the union of the synostosed bones in many places was partial and in a mechanical sense must have been imperfect. It seems probable that the union of the synostosed bones of the cranial vault, particularly at the beginning of the process, may, in some instances, have been imperfect

(Fig. 23). If the line of union of two cranial bones were weaker than the substance of the bone on either side, yielding outward to the increased intracranial pressure in the course of growth would be apt to occur, if it occurred anywhere, along the line of union. The thickening of the bones on the inner surface of the skull near the synostosed suture appears to be analogous to the thickening of the periosteum, developing on the side of the rachitic bone away from the direction of yielding. The curvature of the edges of the bones close to the synostosed suture of such nature that their external surfaces (the sides of the ridge) present a concavity outward is analogous to the inward curvature of the tip end of the shaft of the rib in the severe rachitic malformations of the costochondral junction when yielding inward is taking place.

It is, of course, dangerous to draw inferences from experiments on inanimate objects about phenomena which occur in living tissues. If, however, a patch of some not very bendable material, weakened in the middle by being partially split, is glued to the surface of a moderately distended rubber bag and the bag is then further inflated, the patch yields at the points of the split and along the line of the split is thrown into a ridge.

Though we are by no means certain that the explanation offered for the ridge formation and associated pathological conditions is the correct one, we believe it to be the most probable explanation. We think it must be assumed that the phonomena in question are the the result of forces acting from *within* a cranium in the process of growth, not of extraneous forces operating from *without* according to the explanation of Thoma.

ARE THE MALFORMATIONS GERMINAL IN ORIGIN OR ACQUIRED?

We are now in a position to consider the question: Are the deformities to be regarded as the results of defects inherent in the germ plasm, or as acquired during intra-uterine life through the operation of influences injurious to the embryo?

Are the Malformations Germinal?—At first thought it might appear that the occurrence in combination of malformations situated at widely separated and developmentally independent parts of the body was against an inherited and in favor of an acquired origin. It is evident, however, that combinations of defects may be transmitted in the germ plasm as readily as single defects, or different groups of characteristics, apparently unrelated to each other. There is an exceedingly well known congenital malformation transmitted from one generation to the other, which regularly involves two developmentally independent parts

of the body. We refer to dysostosis cleidocranialis,[88] first described by Marie and Sainton.[89] In this combination of malformations the skull and clavicle are affected. The clavicle either appears to be absent on both sides (more rarely on one side only) or is represented by rudiments. The skull presents a variety of defects—persistence of certain parts in a membranous state, wormian bones, absence or aplasia of the nasal and lacrymal bones, underdevelopment of the skeleton of the face, a narrow and high palate, anomalies in implantation of the teeth, prognathism of the lower jaw, incomplete ossification of the base of the skull, etc. The brachycephaly and the platycephaly are characteristic. Associated defects in other parts of the body have been reported. Thus, it is seen that an inherited condition, dysostosis cleidocranialis, furnishes more than one analogy to the combination of defects under consideration.[90]

When, however, the histories of our cases are searched with the special object of determining an inherited origin, little evidence is forthcoming. There is no record of the existence of acrocephaly alone or with defective development of the extremities in other members of the immediate families, among forbears or collateral branches. Furthermore, with the exception of Dubrisay's patient who had imperforate anus, there is no record of any congenital malformation additional to those of the head and extremities. Moreover, with the exception of the case of Hutchinson [92] (Case 23) (the mother had given birth to a monster said to have had "a head like a cow"), there was no record of congenital malformation in the patient's immediate family, and with the exception of the case of Camus (one distant cousin had ankylosis of the elbows, and a sister of the cousin was an idiot) none in previous generations or in collateral branches. The case histories, therefore, afford almost no evidence in favor of the view that the malformations were inherited according to the mendelian law, and little evidence that they were the product of defective germ plasm.

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88. Hultkrantz, J. W.: (a) Ueber congenitalen Schlüsselbeindefect und damit verbundene Schädelanomalien, Anat. Anz., Jena **15**: 237, 1899. (b) Les altérations du crâne dans la dysostose cléidocranienne, N. iconog. de la Salpêtrière, Par. **21**: 93, 1908.
Sterling, W.: Die tropischen, vegetativen Erkrankungen, Missbildungen und Entwicklungshemmungen des Knochensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **9**: 1, 1914.

89. Marie, P., et Sainton, P.: Observation d'hydrocéphalie héréditaire (père et fils), par vice de développement du crâne et du cerveau, Bull. et mém. Soc. méd. hôp. de Par. **14**: 706, 1897; also: J. de clin. et de thérap. inf., Par. **5**: 405, 1897.

90. Another combination of congenital defects also involving the skeleton and occurring in members of the same family (two families were studied in two generations) has been described as a clinical entity by Dzierzynsky [91] under the title dystrophia periostalis hyperplastica familiaris. It is said to be characterized by an oxycephalic skull and shortening and thickening of the fingers, accompanied by deformities in the joints resulting in limitation of motion. From Dzierzynsky's description and illustrative photographs it is not clear to us that the conditions were well defined or even existed in all the instances in which Dzierzynsky thought they existed. The combination of defects described by Dzierzynsky ought not to be regarded as a clinical entity in the present state of knowledge concerning it. There is the possibility that some of his cases belonged to the group of cases which we are describing.

91. Dzierzynsky, W.: Dystrophia periostalis hyperplastica familiaris, Ztschr. f. d. ges. Neurol. u. Psychiat. **20**: 547, 1913.

92. Hutchinson, R.: Three Cases of Oxycephaly, Proc. Roy. Soc. Med., Lond., Sect. Dis. Child. **3**: 125, 1910. See also Fletcher [Discussion], p. 127.

In putting a valuation, however, on the absence of evidence pointing to an inherited origin it is necessary to remember that in a number of instances the family histories were incomplete and that in no single case had the subject of the malformation had children. Moreover, it must be considered that in an increasing number of instances oxycephaly and scaphocephaly have been reported in more than one child of a family or in two succeeding generations. Symmetrical syndactylism is one of the commonest inherited defects. So far as we are aware, familial syndactylism has never been accompanied by acrocephaly.

The evidences of polydactylism supplied by roentgenograms of the feet in the cases of Davis and Bertolotti and Boidi Trotti cannot be thought to indicate an origin in the germ plasm. Harrison,[45c] for instance, has found that removal of one-half of the fore limb bud in the amblystoma was sometimes followed by syndactylism, incomplete development or absence of a digit, of a hand or forearm but also by reduplication of a digit, of a hand (mirror image reduplication!) or of the entire limb. Also the almost complete reduplication of the deformities of the extremities on the two sides of the body in some of the cases (for example, the deformities of the bones of the feet in the patients of Bertolotti and Boidi Trotti (Case 12), Régis (Case 11) and our own cannot be taken to indicate a defect preexistent in the germ plasm. The injury may have taken place soon after fertilization has been accomplished or at a later period when the embryo was still composed, relatively speaking, of few cells and the cellular precursors of the future limb buds were still aggregated. It is impossible to imagine the production of identical deformities of the hands and feet, after the development of the limb buds had begun, if there is conceived to be on the two sides of the body a perfect correspondence of cell to cell in situation, metabolic state and formative impulse and an application of the injurious influence with a perfect impartiality. The almost complete correspondence of the complicated deformities indicates merely that the injury to the growing embryo must have been done at an early period in its development, if ever done at all.

Are the Malformations Acquired?—Davis saw in the malformations of the joints of the hands and feet in his case, as depicted in roentgenograms, the marks of an inflammatory process. Of course, if traces of inflammation can be identified in the hands and feet, it becomes probable that the malformations of the head as well as those of the extremities had an acquired origin. We are certain, however, that the deformities of the extremities, as revealed through the roentgen ray, do not show the marks of an inflammation and are confident that they exhibit no peculiarities that preclude an origin in defects or eccentricities of the germ plasm.

If the deformities of the skull and extremities themselves fail to give the clue to an acquired origin, the only hope of finding it would seem to lie in reading the riddle of their relationship to each other: Why should the skull and extremities be selected to be affected together? Is it possible to explain their selection on the basis of a common vulnerability?

There is some reason to suppose that the extremities of the fetus, in particular the ends of the extremities, are especially vulnerable. At least in young fetuses aborted in all probability as the result of injurious environmental influences (the abortion is usually ascribed to faulty implantation of the ovum), the extremities are often found to be undersized and the hands and feet retarded in development.[93] The heads of such fetuses also appear abnormal; they are undersized and, relatively speaking, flat. The limbs fail to show, however, on gross inspection, the syndactylous malformation which characterizes the cases of our series. Moreover, the stunting of the head was probably not due to a maldevelopment of the cranium, inasmuch as the latter at the time was composed chiefly of membrane. The brain is known to be a tissue of extreme vulnerability in fetal as well as postfetal life.

Of course, the base of the skull and the extremities are apparently in approximately the same stage of development at a period when the injury to the upper extremity conceivably may have taken place. The base of the skull begins to become differentiated in condensed mesenchyme at about the latter part of the fourth week and the hands and feet[94] at about the fifth and sixth weeks. It is probable that the primordial cranium vault is undergoing analogous changes simultaneously. Accurate information, however, concerning the very early development of the vault of the skull is lacking. We know merely that the membranous layer which forms the roof of the cranial cavity first becomes recognizable at the side of the head in embryos from 9 to 11 mm. long, and gradually extends until it covers the entire vault (Keibel and Mall[95]). If, now, the mesenchymal substance were especially vulnerable at the period when condensation was about to take place, some unfavorable environmental influence acting at the proper moment might injure both skull and extremities. The time relationships in the development of the skull and hands and feet, however, so far as we know them, are not exactly the same. Other parts of the skeleton in approximately the same stage of development at this period apparently are spared. That the mesenchymal substance is especially vulnerable at the time of its condensation or at any period is not proved. In general, mesenchyme and its derivatives, certainly

93. Dr. George L. Streeter, personal communication.
94. The development of the lower extremity lags behind that of the upper.
95. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia and London, J. B. Lippincott Co. **1**: 548, 1909.

the mesenchymal forerunners of the cartilage, and the cartilage itself, appear to be especially resistant. Finally, it is difficult to imagine what kind of an injurious influence could be operative at the same time on the primordia of skull and extremities. That the ends of the limb buds, composed of tissue destined to undergo more complicated development than the rest and farthest removed from the main body mass, might be especially apt to suffer is easy to understand, but not so easy why the cranium should be affected.

It is obviously impossible for us to reach a positive conclusion in regard to the source of origin of the combined malformations. We incline to the view, however, that they originated in defects in the germ plasm itself. The chief reason that we lean toward that hypothesis is because of the cases of oxycephaly and scaphocephaly in which there is the history of a familial incidence.[49, 65a, 92, 96] In a recent case report by Bedell,[96] all three children in one family were scaphocephalic. One of the three children had an abnormal condition of the left elbow [97] suggestive of a unilateral congenital malformation of the bones forming the joint, such as was present on both sides in a number of the cases of our series. If the fetal malformations of the skull characterized by a synostosis of the sutures are germinal in origin, we believe them germinal in origin when accompanied by defective development of the extremities.

SCAPHOCEPHALIC MALFORMATIONS OF THE SKULL ALSO MAY BE ACCOMPANIED BY SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES

To the present point we have considered only acrocephalic malformations of the skull in relation to defective development of the extremities. Defective development of the extremities, however, also accompanies scaphocephalic malformations. We have found one such case in the literature and have ourselves seen one such patient. In the two subjects the scaphocephalic deformity of the cranium was well marked but the malformations of the extremities were extremely slight. In the case reported by Küttner [98] (Case 29) the statement is made that "with the exception of insignificant malformations of the thumbs and great toes the body is essentially normal." [99] In the child seen by us (Case 30, Fig. 25) there was some congenital malformation at the elbow joints which rendered complete extension impossible (Fig. 26). In both cases there was an internal hydrocephalus.

96. Bedell, A. J.: Oxycephalus: Report of Three Cases with Operation in One, J. A. M. A. **68**: 1979 (June 30) 1917. Weiss, L., and Brugger, O.: Oxycephaly and Disease of the Optic Nerve, Arch. Ophth. **24**: 55, 1895. Hanotte, M.: Anatomie pathologique de l'oxycéphalie, Paris, 1898, Masson & Cie., p. 85.

97. "The left elbow joint resisted full extension, and when forcibly extended deflected outward with the inner condyle especially prominent," Bedell,[96] p. 1981.

98. Küttner, H.: Der angeborene Turmschädel, München. med. Wchnschr. **60**: 2209, 1913.

99. Page. 2208.

We are under the impression that severe malformations of the extremities occur less frequently with scaphocephaly than with acrocephaly, and we should judge from the relative numbers of reported cases in the literature, which have come to our notice, that the association with acrocephaly is more frequent than with scaphocephaly. Again, however, we are under the impression that the acrocephalic malformations of the cranium tend to be more extensive than the scaphocephalic malformations. If such be the case, it would be natural to expect more extensive malformations of the extremities in acrocephaly than in scaphocephaly, and that the association might be more common in case of the acrocephaly malformation of the cranium than in the case of the scaphocephalic malformation. We know of no instance of malformation of the extremities in association with trigonocephaly.

Fig. 25.—Photograph of head of W. F., authors' case of scaphocephaly and malformation of elbow joints (Case 30).

THE SIGNIFICANCE TO BE ATTACHED TO THE OCCURRENCE OF MALFORMATIONS IN COMBINATION

It now remains to point out the probable significance to be attached to the occurrence together of the malformations of head and extremities. Is the combination of malformations to be regarded as a clinical entity? Typical acrocephalic and scaphocephalic malformations without malformations of the extremities are frequent and malformations of the extremities similar to those in our series of cases exist apart from malformations of the skull. The association, therefore, is not constant. In spite of that fact, it might still be possible to regard the combination as a clinical entity, if, when the malformations occurred together, they always occurred in some definite form, intermediate

between the malformations of the head with normal extremities on the one side and the malformations of the extremities without cranial defect on the other. The malformation of the extremities, however, shows the greatest variation. In some cases the hands and feet are the seat of most extensive maldevelopment and the bones entering into the formation of the elbow joints and apparently also the shoulder joints are involved. In other cases the malformation is limited to the bones forming the elbows or to most minor defects in the hands and feet. In other words, the malformation of the extremities occurs in a series of grades of severity from the most extensive deformities to the normal condition. There is some indication that the malformation of the head likewise occurs in all

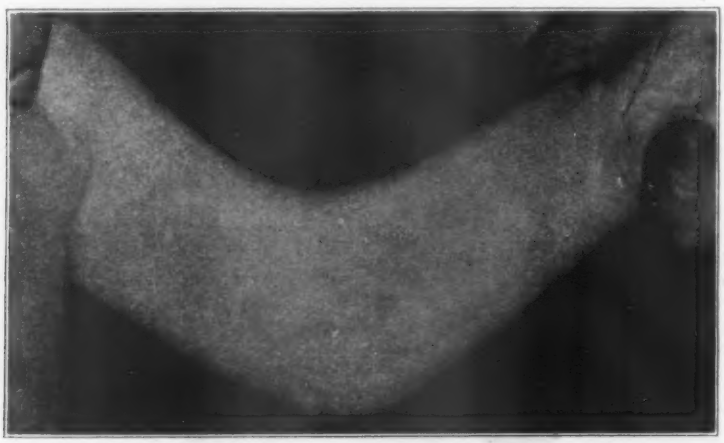

Fig. 26.—Photograph of elbow of W. F., illustrating maximum degree of extension obtainable (Case 30).

grades of severity from the most extensive to a condition differing but slightly from the normal. In the present state of knowledge, therefore, it seems unjustifiable to regard the combination of malformations of head and extremities as a clinical entity. The significance of their occurrence together appears to be merely an inconstant association. The malformation seems to have the special tendency, when appearing in the head, to appear also in the extremities. We believe, therefore, that it is necessary to think of acrocephalic and scaphocephalic malformations existing alone and acrocephalic and scaphocephalic malformations existing in combination with symmetrically distributed malformations of the extremities, not as distinct things, but as different expressions of one and the same thing. Accordingly we have felt obliged to discard the title, "acrocephalosyndactylism." [100]

100. The title, "acrocephalosyndactylism," does not include those cases in which the malformation of the extremities was limited to parts other than the hands and feet.

We believe that the association of deformities of the extremities with deformities of the skull of the kind under consideration is more frequent than hitherto has been thought or than statistics indicate, and that in some subjects of oxy- and scaphocephaly unsuspected maldevelopments of the extremities will be brought to light if the possibility of their occurrence is kept in mind. We are not certain that more careful studies may not reveal in association with the maldevelopments of the skull maldevelopments in yet other parts of the skeleton than the extremities.

In conclusion, we wish to express our indebtedness to Dr. Warren Lewis and Dr. George L. Streeter of the Department of Embryology, Carnegie Institute of Washington, for their suggestion of ideas, their constant interest, and their many acts of courtesy. Without their cooperation the study in its present form would have been impossible. We wish to express our thanks to Dr. A. H. Schultz of the same department, for his great kindness in taking the measurements and for his advice on a number of occasions. We wish also to express our thanks to Dr. J. W. Pierson of the Department of Roentgenology for assistance in the interpretation of the roentgenograms.

ABSTRACTS OF CASES

I. CASES OF ACROBRACHYCEPHALY WITH COMPLETE OR ALMOST COMPLETE SYNDACTYLISM

(Cases 1 to 20, inclusive)

CASE 1.—Troquart,[28] 1886. New-born child, delivered at term after normal labor. Mother 33, father 31 years old. Both parents always well; neither they nor grandparents deformed. Hands of baby in condition of almost complete syndactylism apparently with some osseous union. Thumbs separate. Feet showed same condition. Head voluminous; frontal bosses prominent; anterior fontanel extended almost to bridge of nose. Partial separation of soft palate. Dudon, in discussion of Troquart's case, referred to sutures as open, and stated that aspect of child was that of hydrocephalic. (Description meager; no photographs; no roentgenograms.)

CASE 2.—Beno,[101] 1886. Healthy, well nourished girl, 18 months old. No history of malformation in antecedents. Head greatly flattened from before backward. Sutures closed. Forehead prominent in upper part. Eyes protruded slightly. Dentition normal. Feet in condition of complete syndactylism without bony union, not interfering with walking. Fngers and thumbs of both hands fused into single mass. On palmar surface of hands tips of three fingers marked out by shallow grooves; on dorsal surface all fingers delineated by longitudinal grooves. One nail served for second, third and fourth fingers, and rudimentary nail for fifth. All metacarpal bones and phalanges seemed to occupy normal positions and to be unattached to each other except terminal phalanges, which appeared joined into single mass, and except metacarpal bones of thumbs which were joined to corresponding index fingers by bony and fibrous union. (Description brief; no photographs; no roentgenograms.)

CASE 3.—Magnan and Galippe,[11] 1892. Man, 35 years old. Only statement made in regard to family history is that on maternal side there was history of alcoholism and nervous disorders. Head flattened in front and behind and asymmetrical. Right frontal eminence exceedingly prominent, left flattened; left mastoid region prominent, right poorly developed. Forehead broad; much higher on right side than on left; traversed in middle portion by horizontal

101. Beno, J.: Essai sur la syndactylie congénitale, Nancy, 1886, No. 238.

groove, above which in median line was well marked prominence. Occipital protuberance unusually large. Head particularly high about bregma so that "certain degree of acrocephaly" existed. Face appeared very flat, cheeks sunken. Nose large, thick, deviated to left. Nostrils small. Eyeballs so prominent they looked pedunculated, and protruded 1 cm. beyond plane of forehead. Sclera visible, especially inferiorly. Palpebral fissures directed downward and outward. Mouth distorted. Alveolar processes close together, converging anteriorly. Palate narrow, highly arched; soft palate exceedingly long, uvula bifid. Lower jaw narrow, as if compressed laterally. Teeth abnormally placed. Complete syndactylism of feet, and hands with exception of terminal phalanges of little fingers which were separate. Metacarpal bones of thumb, index and middle fingers could be distinguished and were not united, but those of third and fourth fingers were joined together behind. All phalanges seem to have been present, but last two phalanges of ring finger atrophic. Separate nails for thumb and little finger, but nails for index and middle fingers fused; rudimentary nail for ring finger. Deformity of left hand corresponded in general to that of right. Separate nail for great toe but nails of other toes united at edges. Arms not normal for complete extension, supination and certain other movements impossible. (Well described; photographs of whole body and of palate on page 19 of Gadelius' report; no roentgenograms.)

CASES 4 AND 5. — Wheaton,[17] 1894. One case was illegitimate first child, aged 3 months at time of death; other, fourteenth child in healthy family dying when 2 months old. Deformities almost identical. We quote Wheaton's report:

> The deformity of the crania is characterized by arrest of development of the base of the skull in an anteroposterior direction, the fossae at the base of the skull being markedly contracted in an anteroposterior direction, but of about normal width from side to side. The posterior fossa of the skull is especially narrow from before backwards, and the occipital bones are extremely small. The basi-occipital bone in one case is only one eighth of an inch in diameter and in the other case this portion of the occipital bone is united to the basisphenoid by firm bony union. The occipitofrontal diameter of the crania is only four inches in each case, whereas in the case of a new-born infant this diameter is four and a half inches. The biparietal diameter of the skull is also almost exactly four inches in each case, so that the cranial cavity is almost perfectly globular in shape. A continuous suture extends from the posterior fontanel to the root of the nose in both cases, and the frontal suture is especially wide, measuring an inch and a quarter in a transverse direction. There are wormian bones in the posterior fontanels in both specimens, and in the frontal suture in addition in one specimen. The margins of the bones bounding the sutures and fontanels are irregular and have a crenated outline; the frontal and parietal bones in both specimens present numerous pits or elliptical depressions on their inner surfaces, where the bone is extemely thin, and in a few places bony deposit over these areas is absent entirely. These areas can be well seen when the bones are held in front of a light. During life the bones of the vault of the skull could be indented with the finger. With regard to the condition of the hands and feet, in both children the fingers of both hands were fused into one mass, but the thumbs were separated. The hands were not dissected, but in one child the metacarpal bones and phalanges of the two middle fingers appeared to be fused into one bone, and in the other case there were only four metacarpal bones and the second finger had no phalanges. The nails of the two middle fingers of both hands were fused into one in the case of one infant, and those of the three inner fingers were fused in the case of the other. All the toes were fused together in one child, but in the other the big toes were separate. The nails of the toes were separate in both cases. Talipes varus was present in both.
>
> During life the children presented the appearances of cases of hydrocephalus, except that there was no enlargement of the skull; but on postmortem examination no accumulation of fluid was found either on the surface of the brain or in the cerebral ventricles.
>
> Owing to the defective development of the occipital portion of the skull, the back of the head appeared to be nearly flush with the nape of the neck, the fontanels and sutures were tense, and the pulsation of the brain could be seen and felt through them. The bones of the face appeared to be normal, with the exception of those of the nose, which was very flat and depressed. The skin of the body, and especially that of the face, was very much wrinkled and of a yellowish color, and both children suffered from snuffles, the ears were wrinkled and small, and the tongue constantly protruded — so that the children had a very repulsive appearance. The children could not suck, and were fed by hand. Both children died from asthenia, without the development of any noteworthy symptoms.
>
> On postmortem examination the brain appeared to be compressed, and bulged considerably when the dura mater was incised; but, as before mentioned, there was no accumulation of fluid inside the skull. The convolutions were flattened as if from pressure, and the anteroposterior diameter of the brain remarkably shortened, in a manner corresponding with the shape of the cranial cavity. There was a marked want of development of the occipital lobes of the brain, which were so small that the cerebellum was almost entirely uncovered. The frontal lobes were also small and pointed. No important convolutions appeared to be absent, however. No other changes were found in the bodies except enlargment of the liver and spleen, in both instances the latter organ being tough and firm, evidently from excess of fibrous tissue. There were no signs of rickets.

(Necropsies; no photographs; no roentgenograms.)

CASE 6.—Maygrier,[19] Fournier,[20] 1898. New-born girl. Mother had borne four healthy children to first husband. Second husband aged 35 years, had acquired syphilis at 19. Following marriage to second husband, two miscarriages in succession, next an apparently healthy child dying from intercurrent illness at 3½ years, finally patient. In second month of pregnancy with patient, abdomen noticed to be unduly large; by seventh it began to assume extremely large proportions. Labor occurred at term; unusually large quantity amniotic fluid. Birth instrumental. Forehead of child exceedingly prominent, protruding forward in middle part 2 cm. in form of very large tumor elongated from above downward, beginning at anterior fontanel and ending abruptly just above root of nose; at sides limited by inner borders frontal bones. Latter separated distance of 2 cm. and apparently displaced forward and outward by tumor. Head flattened in both temporal regions and behind to such extent that back of head appeared in same plane as neck. Sagittal suture narrow in anterior part but in middle broadened so as to form accessory lozenge-shaped fontanel between anterior and posterior fontanel. Anterior fontanel 4 cm. wide; posterior extremely wide. Eyes, unusually prominent, appeared more so than actually because of depression of superciliary arches. Palate formed high arch. All four extremities well formed with exception of hands and feet. Malformations hands limited to fingers. Thumbs flattened and shaped like spatulae, appeared dislocated internally and lay flexed across hollow of palm. Integrity movements thumbs preserved. Four fingers united in entire extent. Phalanges index, middle and ring fingers terminate in single mass of bone, surmounted by single nail; the proximal and middle phalanges separate. Phalanges of little finger, which has separate nail, not joined to others. Toes apparently united only by soft parts; each has nail. Child living one month after birth. (Magrier and Fournier each reported this case separately; photograph in Fournier's report; no roentgenograms.)

CASE 7.—Ireland,[21] 1898. "Young man" (age not stated); fourth of eight children. Brothers and sisters healthy. No record nervous disorders or deformities in family. Slow in learning to walk and speak. At 14 sent to school for imbeciles where he learned joiners' work. Apparently under normal in intelligence. Head prolonged upward, narrow from before backward; circumference 55 cm. Eyes prominent, injected from imperfect closure of lids. Eyeballs have divergent axes. Skin thick, pustulated; deep furrows across forehead. Nose "shapeless." Lips broad. Mucous membrane of palate divided by longitudinal folds with apparently deficiency of palate bone behind. "The feet are short and broad, the first metatarsal bone is wanting on both feet and the first phalanx of the great toe is implanted in the angle between the second metatarsal and the internal cuneiform. The four outer toes have completely grown together with the soft parts. The feet are short and broad with high insteps." Hands, as shown in photographs, appear completely syndactylous. Arms are obviously abnormal for they reach only to level of pelvis. (Description fragmentary; no roentgenograms; photographs of front view of head and of hands in Ireland's book; these photographs and a lateral view of head and of whole figure in Gadelius' report, p. 18.)

CASE 8.—Dubrisay,[24] 1898. New-born girl; weight, 3,150 gm.; length, 45 cm. Family history negative; no record of any malformation among antecedents or collaterals. Excess of amniotic fluid present at birth. Back of head normal. Anterior part projected forward; maximum deformity at summit frontal bone. Frontal bosses prominent; metopic suture 2 cm. wide, continuous with anterior fontanel. Root of nose depressed. Eyes prominent. Buccal cavity normal. Extremities well formed, with exception hands and feet. Metacarpal bones separated by well defined depressions; fingers fused into cone-shaped mass. No division between phalanges determined. At distal end of cone-shaped mass skin replaced by two nails unequal in size, one corresponding apparently to nail of thumb, other to nails of fingers. Both

hands affected in same way. Toes formed single mass but nails formed uninterrupted band extending from one side to other. Roentgenograms of feet and hands showed metacarpals normal but phalanges replaced by two masses of bone, separate, apparently representing fused phalanges; metatarsal bones united in certain places. In addition to deformities enumerated imperforate anus. Died six days after birth. (Necropsy, but skull and extremities not examined. Description very poor. Photographs; roentgenograms of extremities but not of head.)

CASE 9.—Camus,[21] 1903. Boy 10½ years old, oldest of three children; other two normal. Family history negative except one distant cousin had congenital ankylosis of elbows and sister of cousin idiot. Head much prolonged in vertical direction but short, flattened at sides. Forehead, exceptionally high, presented in median line keel-shaped enlargement especially prominent in lower part; in contrast frontal eminences depressed. Supra-orbital arches prominent. Parietal bones extended abnormally far upward; not convex as usual; separated from squamous portions temporal bones which seemed very prominent by depression. Bones of vault of skull thick and resonant. Face had flattened appearance through atrophy of malar and superior maxillary bones. Nose short, not very prominent, deviated to left. Eyes protruded; palpebral axes oblique from within outward and downward. Examination buccal cavity disclosed atresia superior maxilla which, maximal anteriorly, was cause of well developed acrognathia. Alveolar processes and mucous membranes covering them hypertrophic in region of incisor teeth and joined in such way as to produce recess in anterior portion of roof of mouth. Soft palate cleft. Hands showed syndactylism of all four fingers but with thumbs free. Latter had own nails but phalanges fused into single place. Fingers united in such way as to form spoon-shaped mass. Ring, middle and index fingers had single nail, and distal two phalanges of all three appeared fused. Fifth finger having nail joined to others only through union of soft parts. Feet showed complete syndactylism consisting in fusion of soft parts alone. Each toe had own nail. Ankylosis of elbow joint in semiflexion and pronation ascribed to "synarthrosis" of humerus and radius, with hypertrophy of head of latter. (Fair description; no photographs; no roentgenograms.)

CASE 10.—Apert,[1] 1906. Girl, aged 5 months. No information regarding child's antecedents or mother's pregnancy. Head very high; forehead ascends vertically but rounded and bulging forward beyond vertical in upper half; across middle portion horizontal groove. Superciliary ridges prominent. Eyeballs protruded. Anterior fontanel occupied summit of head. Immediately behind anterior fontanel head fell off abruptly to neck, so that occiput perfectly flat. Palate cleft in posterior part; uvula bifid. Thumb of left hand almost normal but spatula-shaped, lay transversely across hand. Three other fingers besides thumb; outer two firmly united, apparently by bony union; nails fused. Inner one joined to other two only by soft parts; moveable independently of latter. Three fingers of this hand almost immobile on metacarpals, and ankylosed at phalangeal joints. Deformity of left hand almost exactly like that of right, except little finger entirely free. Right foot had four toes, of which great toe short, flat, mobile, two middle toes fused, immobile, little toe flat, mobile, provided with large Hippocratic type of nail; left foot had five toes joined together, big toe loosely, other four firmly. Four nails fused at points of contact. (Incompletely described; no photographs; no roentgenograms.)

CASE 11.—Régis,[22] 1914. Under legend "Dégénérée avec stigmates physique multiples de dégénérescence" author publishes photograph of girl, certainly 16 years old, showing characteristic deformity of head and extremities. Top of head hidden by cap, but forehead high, face broad, eyes far apart and protruding, especially left, and having divergent axes. General contour of face typical. Hands and feet syndactylous. Thumbs free, but fingers united. Great toes free, but others joined together. Roentgenograms indicate malformation

more extensive in hands than feet. Metacarpal bones of little and ring fingers represented by thick, irregularly shaped, single bone. Phalanges consist of single bones about two-thirds length of metacarpal bones which incline toward each other and are fused at distal extremities. Phalanges of thumb represented by single nodular mass which joins metacarpal bones on inner side of distal extremity. Bones of carpus and wrist cannot well be seen. Phalanges and metatarsals of feet not united laterally. Metatarsal bones abnormally formed, that of great toe being huge. Feet broad. Metatarsal of great toe directed forward and inward, metatarsal of little toe forward and outward, so giving to foot fan shaped appearance. Little toe has long proximal and short distal phalanx, others have single phalanges.

Evidences of degeneration cited are: Obesity, thickness of hair, macrocephaly, asymmetry of face, exophthalmus, flattening of root of nose, narrow and highly arched palate, absence of soft palate, anomalies of implantation and form of teeth, prognathism, syndactyly, enlargements of breasts. (Photograph of whole body; roentgenograms of hands and feet.)

Case 12.—Bertolotti and Boidi Trotti,[12b, c] 1915. Girl 5 years old. Father, mother, two sisters, one brother well. One sister dead of "meningitis." No history syphilis. No deformities similar to those of patient known in family. "Abundant" amniotic fluid present at birth. Head oxycephalic; vertical diameter greatly increased; sagittal diameter comparatively diminished. Frontal bone very high with deep transverse groove in middle portion above protruding superciliary arches. Forehead bulges markedly above transverse groove. Bregma at apex of skull in same vertical plane with face. Skull slopes downward from bregma to occiput. Skull protuberant in temporal and constricted in mastoid regions. No occipital prominence. Occiput neck in same vertical plane. Metopic suture closed; synostosis marked by prominent ridge. Face broad and full in upper and zygomatic portions, decidedly pinched inferiorly. Eyes obliquely placed, palpebral fissures directed downwardly and outwardly from nose at angle of 120 degrees. Exophthalmus. Optic neuritis; margins disks blurred; veins large and tortuous. Acuity vision diminished. Ears large, regular in form. Otoscopic examination reveals no abnormality. Acuity hearing diminished, due, it is stated, to some defect in central nervous connections. Middle portion upper lip prominent; angles mouth depressed. Lower lip retracted; chin recessive. Marked atresia of maxilla. Palatine vault high and angular. Uvula and soft palate divided but palatine eminences seem united. Dentition very irregular; some incisors directly back of others. Palatine tonsils large. Adenoids present. Nasal fossae narrow, deviation to left. Nasal obstruction. Circumference head at level superciliary arches, 49 cm., at transverse frontal groove, 47 cm. Maximal sagittal, 13 cm., maximal transverse 15 cm. Cephalic index, 115. Roentgenographic studies of cranium show vault considerably thinned; digitations marked especially in frontal region. Cranial vault very high, relatively short in sagittal diameter. Base "scooped out" with wings of sphenoid more nearly vertical than usual and median cerebral fossae very deep. Orbital fossae shallow; vertical diameters greater than horizontal. Sphenoidal angle, 168 degrees instead of normal—132 degrees. Diastasis of suture between body of sphenoid and basi-occipital bone.

Hands show five digits formed from single spoon-shaped mass as result of operation. Digits separate for only short distance distally; simply grooved off from each other proximally. Body of hand narrow; digits irregular and bulbous, especially at ends. Fingers flare in fan-like manner. Each digit has own nail; nails large, hypertrophic. Before operation nails, except nail of thumb, completely fused. Roentgenographic study shows partial ossification of carpal bones (six nuclei on right, five on left), partial fusion of fourth and fifth metacarpals and normal metacarpal epiphyses. Thumb has but one phalanx; three phalanges for each finger, although phalanges are fused in several digits. Two distal phalanges very large and bizarre in shape; epiphyses also very large. Limitation of movement at scapulo-humeral articulations and elbows; synostosis between radius and ulna at elbow.

Feet show complete syndactylism (no surgical interference). Slight grooves between first, second, fourth and fifth toes. Nail for great toe divided; four other nails on each foot. Ossification of tarsus normal but some of the bones abnormal in shape, size and relations. Some metatarsals bifurcated and fused with neighboring bones. Phalanges grossly misshapen; apparently only two for each digit. Large epiphyses.

Intelligence average or even above. Evidences of rachitis. (Well described; photographs and roentgenograms of head, hands and feet.)

CASE 13.—Davis,[14] 1915. Father and mother living, well; three other children, all healthy; two miscarriages. No mention made of malformations in family. Patient, girl, 3½ years of age; born at term without instruments, "puny" until 1½ years old; probably mentally retarded. Head shortened in sagittal diameter; frontomental, bitemporal and bizygomatic diameters increased; shape of head that of foursided pyramid with apex in region of lambda and base formed by diamond-shaped face; face broad, flat; forehead high, precipitous; superciliary ridges highly arched and flattened. Bridge of nose "low," and bulging. Ten teeth, well formed but irregularly placed. Hard palate highly and sharply arched; apex of inverted "V" near soft palate; shelf-like projection along alveolar margins of maxilla. Proptosis. Ophthalmoscopic examination shows media clear, nerve head gray, margins of disks blurred; apparently some swelling of disks but could not be measured; retinal vessels slightly tortuous. Measurements: circumference (fronto-occipital), 48 cm.; fronto-occipital diameter, 15 cm.; bitemporal, 12 cm.; biparietal, 14.5 cm.; length of frontal suture, 9 cm.; width of frontal suture, 4 cm.; cephalic index, 96.6. Photographs after plastic operations show three digits on left hand, three on right with shadows suggestive of fourth; medial digit in line with axis of arm; lateral digits flare out from this axis; digits fused at base and only free for short distance distally; they have constricted, pinched off appearance at metacarpal phalangeal junction in comparison with broader body of hand; hands operated on during first year; all digits of each hand were so completely fused that no line of cleavage could be made out. Feet show no abnormality above metatarsophalangeal articulations; no digits; nails continuous with each other: five on left foot, four on right: great toe portion stands out prominently and is turned up dorsally as is whole phalangeal region of foot. Roentgenograms. Head: sagittal, lambdoid and coronal sutures closed; metopic suture enormously dilated: sella turcica deepened and broadened: orbits fore-shortened: digital impressions marked in occipital and posterior positions of parietal bones. Right hand. Five metacarpals, fourth and fifth partially fused: five digits: for thumb one bone; for second digit three bones, terminal one being curved back and possibly belonging to thumb: bones of third and fourth digits closely opposed and joints replaced by bone: three phalanges for fifth finger, second and third falling laterally. Left hand. Five metacarpals, fourth and fifth partially fused. No bone shadows for thumb, second, third and fourth fingers "present bone shadows suggestive of a phalangeal complement for four fingers. This fact probably accounts for the bones missing from the thumb. These bones irregularly fused into bony plate with apparently obliteration of proximal interphalangeal joints. In little finger shadows of but two bones. There is gap at position which the middle phalanx should occupy." Right foot. Tarsal bones normal: six metatarsals; first and second partially fused. "The first is incomplete proximally, while distally it appears to extend without division or other trace of phalanges into the great toe." Fourth and fifth metatarsals partially fused. Phalangeal rudiments for six toes. Left foot. Similar to right; union between first and second metatarsals more "intimate"; no other union between metatarsals. First and second phalangeal rudiments closely united. (Good description: photographs and roentgenograms of head, hands and feet.)

CASE 14.—Gadelius,[20] 1915. Man, 24 years old; illegitimate. Parents not deformed. Subsequent to birth of patient mother married another man and

bore normal child. Deformities fully developed at birth. Head "cylindrical," flattened from before backward and prolonged upward. Circumference at root of nose, 54.3 cm. Fronto-occipital diameter, 16.5 cm.; biparietal, 15.5 cm. Cranial index, 94. Eyeballs protruding in downward outward direction; divergent; right eye does not coordinate with left. Nose short, broad. Prognathism lower jaw. Hard palate cleft; soft palate intact. Teeth regularly placed. Hands and feet syndactylous. Middle three fingers form single mass; thumbs free, little fingers partially free. Roentgenograms of hands show metacarpal bones separate from each other, approximating normal in contour. Little fingers have three bones, proximal abnormally long, middle abnormally short and thick; ring fingers two bones, proximal almost as long as metacarpal, obviously representing proximal and middle phalanges fused; middle finger of right hand single irregularly shaped bone, obviously representing all three phalanges; middle finger of left hand to be described presently; index fingers have two bones, distal representing two distal phalanges fused. Single nodular mass of bone represents phalanges of thumb, it joins metacarpal bone at inner side of its distal extremity. Bones of index, middle and ring fingers, right hand, fused together distally from point corresponding to junction of middle and proximal phalanges. Index finger of right hand connected with ring finger by horizontal bridge of bone of about same thickness as phalanx. Bone representing proximal and middle phalanges of middle finger directed downward and inward overlies long bone representing proximal and middle phalanges of ring finger; bone representing distal phalanx of middle finger, not connected with bone representing proximal and middle phalanges, projects downward from bridge of bone just mentioned. Toes partially syndactylous. Roentgenograms show syndactylism of toes limited to soft parts. Metatarsal bones approximately normal with exception that of great toe, which is much thickened and irregularly shaped. Little and fourth toes have two bones each, proximal probably representing first two phalanges; third and second toes single bones, obviously representing all three phalanges; great toe one large irregular mass of bone, in excavation in side of which lies loose fragment. Foot extremely broad. Metacarpal and phalanx of great toe directed forward and inward. Mental development lower limits of normal. (Photographs of whole body and of hands: roentgenograms of hands and of one foot.)

Case 15.—Gadelius, 1915. A girl, age not given, apparently about 6 years old when examination was made. Parents healthy; not deformed. Patient eleventh child. Brothers and sisters normally formed. Development somewhat retarded. Walked at 2 years. At 6 years sent to home for defective and crippled children. On examination, striking features head and extremities. Head high. Circumference, 47 cm. Fronto-occipital diameter, 16 cm.; biparietal, 14.5 cm., cranial index, 90. Eyes far apart. Marked proptosis. Horizontal axes of eyes directed downward and outward. Palate cleft. Syndactylism of hands and feet but thumbs and great toes free. Roentgenograms of hands indicate that phalanges are represented by single bones fused together distally. Metacarpal bones apparently separate. Died at age of 12 years. (Photograph of whole body: roentgenograms of hands.)

Case 16.—Gadelius, 1915. A boy, age not given, apparently about 8 years old when examination was made. Four brothers and sisters. All members of family, including parents, healthy, normally formed. Head shows marked brachy and acrocephaly. Marked exophthalmos with characteristic rotation eyeballs; axes in downward and outward direction; external strabismus. Palate cleft. Breathes with mouth open. Eyes inflamed; cornial ulcers. Feebleminded. Syndactylism of hands and feet but with thumbs free and great toes partially free. Roentgenograms indicate that metacarpal bones, though not normally formed, are separate from each other. Phalanges, including those of thumb represented by single bones. Those of fingers fused together distally into single mass. Roentgenograms of foot indicates less marked degree of malformation. Phalanges represented by two bones each with exception of

great toe which is represented by large mass of bone shaped like horse shoe. Phalanges of toes not united laterally. Patient died at 8 years. (Necropsy, but no report of findings in skull or extremities; hypophysis studied microscopically and found to be normal: photographs of head and hands: roentgenograms of one hand and one foot.)

CASE 17.—Gadelius, 1915. Woman, 25 years old, eldest of three children. All members of family, including parents, normally formed. Marked acrocephaly and brachycephaly. Exophthalmos with peculiar rotation of eyes in downward and outward direction. Cleft palate. Prognathism of lower jaw. Abnormalities in implantation of teeth. Syndactylism of all four extremities. Intelligence subnormal. (Meager description; photographs of head, palate, hands and feet; no roentgenograms.)

CASE 18.—DeSalterain,[15] 1917. Negress, 8 years old. Parents healthy. Eight children previous to birth of patient, of which four had died, one at birth, one during first year (unknown cause), other two in adult life. No member of family with exception of patient deformed. Born at term in mother's forty-sixth year. Deformities head and extremities present at birth. Except for convulsions at 6 years and again at 7 years always well. Striking feature shape of head. Latter "prolonged upward," markedly shortened from before backward. Length and breadth, each 16 cm.; cranial index, 100, circumference, 51 cm. Glabella depressed. External occipital protuberance not felt. Exophthalmus especially marked on right side. Left fundus shows pallor disk and enlargement in transverse direction: right not visible on account staphyloma. Hard palate highly arched, marked by central longitudinal ridge. Adenoids hypertrophied, tonsils present. Syndactylism both hands. No statement made to indicate if feet similarly affected. Height normal. Mental development backward. Roentgenogram of skull said to have shown prematurely ossified sutures, deepening of fossae in addition to brachycephaly. Wassermann negative. (Photograph of head: roentgenogram of head referred to but not shown: roentgenograms of extremities.)

CASE 19.—Ruh,[16] 1916. Father and mother living; two other children, living and well; no miscarriages, no history of syphilis; no malformation in "any member of the family" (report not specific); deformity in patient attributed to "maternal impression." Patient a boy, 6 months of age; admitted to hospital for "cold in the head"; born at term; weight, 8 pounds; delivery normal but child resuscitated with difficulty; weaned at 2 weeks because difficulty in breathing prevented nursing. Well nourished child with normal mentality. Head shows increase in measurement from nasion to inion: biparietal and anteroposterior diameters decreased, whereas bitemporal and bizygomatic diameters increased. Circumference (fronto-occipital), 38 cm.; fronto-occipital diameter, 11 cm.; bitemporal, 11.5 cm.; biparietal, 10.5 cm.; cephalic index, 95.6. Pronounced bulging of forehead in superior portion and flattening of superciliary arches above which is transverse groove. Occipital region much flattened; no external occipital protuberance. Anterior and posterior fontanels, coronal, sagittal and lambdoid sutures open: metopic suture replaced by ridge-like bony prominence. Veins of scalp, especially temporal much distended. Ears large; external auditory canal compressed anteroposteriorly so that examination of ear drums is impossible; sense of hearing acute. Eyes obliquely placed so that external canthi lower than inner: proptosis. Base of nose depressed. Palate narrow, highly and acutely arched; mouth kept open; tongue larger than normal, protrudes because of shortening of pharynx; uvula normal. Roentgenogram is said to show digital impressions in frontal and parietal regions. Hands: complete syndactylism, excepting thumbs, partially flexed at the metacarpophalangeal joints: palms spoon-shaped: nails fused. Roentgenogram of right hand shows absence terminal phalanges: metacarpals not fused: considerable ossification of unciform and os magnum.

In left hand fusion of fourth and fifth metacarpals. Feet show complete syndactylism including great toes. Nails not completely fused as in hands. Roentgenogram right foot shows no terminal phalanges: first digit larger than normal and on inner side notch—at base of second metatarsal large tuberosity. Roentgenogram left foot shows absence terminal phalanges: first digit much larger than normal. Near base second digit large sesamoid bone: first and second metatarsal bones united near bases. (Photographs of head and extremities: roentgenograms of feet and hands: roentgenogram of head referred to but not shown.)

TABLE 4.—MEASUREMENTS OF SKULL AS COMPARED WITH MEASUREMENTS OF SKULL OF NORMAL NEW-BORN CHILD

	Skull of Rieping's Case	Skull of Normal New-Born Child*
Suboccipital bregmatic diameter	90 mm.	90 mm.
Fronto-occipital diameter	80 mm.	110 mm.
Mento-occipital diameter	110 mm.	130 mm.
Vertical diameter (vertex to base)	105 mm.	95 mm.
Biparietal diameter	60 mm.	90 mm.
Bitemporal diameter	95 mm.	80 mm.
Projective ear height (tragus-vertex)	95 mm.	80 mm.
Intermalar breadth	50 mm.	65 mm.
Maximum horizontal circumference	31 cm.	34 cm.
Maximum vertical circumference	34 cm.	35 cm.
Length-breadth index	87.5	72.72
Depth of orbital fossae	18 mm.	28 mm.†
Depth of cerebral fossae (measured from highest point of cranium)		
Anterior cerebral fossa	19 cm.	19 cm.
Middle cerebral fossa	23 cm.	22 cm.
Posterior cerebral fossa	28.5 cm.	26.5 cm.
Anterior border of crista galli to posterior border of posterior fontanel	16 cm.	21 cm.

* Apparently these measurements are quoted from Schauta.
† Apparently these measurements were made by Rieping on a normal skull. [Necropsy: photographs of head, front and lateral views. No roentgenograms].

CASE 20.—Rieping,[15] 1919. Family history not known. Child seen only after death. Body normal everywhere with exception of head and extremities. Head oxycephalic. As seen from in front after removal of scalp (photograph), face appears as if surmounted by casque helmet. Highest point of head forms a peak situated about midway between fontanels and immediately above external auditory meatus. Occipital portion of head less prominent than normal but not flat as in majority of cases. Anterior fontanel is 10 mm. long and 20 mm. wide. Posterior fontanel much larger than anterior; shaped like equilateral triangle, measuring 40 mm. across base, and 50 c.c. in length (the perpendicular). Metopic suture "wide open" from level of superciliary ridges to anterior fontanel, from which it is separated by small bony bridge. It contains wormian bone 40 mm. long and 6 mm. wide. Sagittal suture divided into limbs by oxycephalic peak. Anterior limb exhibits interserration of opposed edges of parietal bones, which are overlapped and raised into keel-shaped ridge (crista sagittalis). Posterior limb shows interlocking in upper part but in lower part spreads open as it passes into posterior fontanel. (For continuation of description of skull, see pages 259 and 260.) Eyes not described. Lidslits, however, slant in characteristic manner from within outward and downward (photograph) and prominence of lids makes it almost certain that eyeballs beneath protruded. Hard palate highly arched but not cleft. Uvula and soft palate normal. Fingers and toes completely united. Nail formation irregular. No roentgenographic studies or dissections of hands or feet.

II. CASES OF ACROBRACHYCEPHALY WITH RELATIVELY SLIGHT DEFORMITIES OF THE EXTREMITIES

(Cases 21 to 24, inclusive.)

CASE 21.—Dodd and McMullen,[18] 1903. Boy, 7 years old. Deformities present at birth. Third child in family of four; others healthy, normally developed, intelligent. No history of syphilis in parents or of deformity in any of patient's relatives. Small child. Head shows remarkable projection upward of anterior part of cranium, and marked bulgings in temporal regions. Face broad and flat. Eyes very prominent and widely separated. Nose small, bridge short and narrow. Head, 48.5 cm. in circumference; anteroposterior diameter, 15.6 cm.; bitemporal, 14.2 cm.; height of face, chin to hair, 14.5 cm. Cranial index, 91.7. Most remarkable features of measurements are great excess in height and width. Forehead very high and vertical in middle line. Distinct depression above outer part of superciliary ridge. Face slightly asymmetrical. Superior maxillae poorly developed. Mouth kept open. Palate narrow, very highly arched; premaxillae deficient. "On both sides, on extension and supination, of forearm, the head of the radius becomes sublaxated forward, apparently owing to laxity of ligaments. On flexion the head of the bone returns into place." "But in this case it appears probable that the slight defect is congenital, as it is symmetrical and associated with developmental defects in other parts of the body." Phalanges of great toes abnormally broad. Slight hallux varus. Interphalangeal joints ankylosed with some inversion Arches of feet flat. Knee-joints rather large. Slight genuvalgum. (Photographs of front and side of head; no roentgenograms.)

CASE 22.—Hutchinson,[22] 1910. Girl, age 1 year, first child. Full term; at time of birth mother aged 25 years. Oxycephalic-shaped head; circumference, 16.5 inches. Suture between frontal bones open to root of nose; coronal and sagittal sutures closed. Eyes wide apart, divergent; slight nystagmus, both rotary and lateral; "disks pale, atrophic." Hands show webbing between ring and middle fingers on left side, and to less degree on right; phalanges normal. Toes rather irregularly arranged. Some evidence of adenoids. Viscera healthy. Mental condition doubtful. (Description fragmentary; photograph of front view of head; no roentgenograms.)

CASE 23.—Hutchison, 1910. Girl, aged 5 years. Youngest of seven; others normal; two died in infancy. Three miscarriages; one monster with "head like a cow." Full term; always healthy. Oxycephalic head with flat occiput and ridge up middle of forehead. Exophthalmus; eyes directed outward; pupils eccentric, upward and inward. Right responds well to light, left sluggish; disks atrophic, sight defective; adenoid facies; high arched palate. "Hands show short (bifid) thumbs, only two phalanges in left index; one long and a short terminal. Toes webbed, and great toes very short." Impossible completely to extend elbows. Viscera normal. Mental condition normal. (Description fragmentary; photograph of front view of head; no roentgenograms.)

CASE 24.—Cameron,[28] 1918. Baby (sex not stated), 8 weeks old. One other child in family healthy. No affection similar to patient's appears in family history. Deformities present at birth. Skull shows "the ordinary appearance of mild oxycephaly." Eyes prominent. Eye grounds normal. Symmetrical deformity of extremities which consists apparently in "giant great toes and giant thumbs consisting of the union of two separate thumbs and two separate toes." (Inadequate description; no photographs; no roentgenograms. The author states he has seen one other case exactly similar to the one described.)

III. CASES OF ACROBRACHYCEPHALY WITH DEFORMITIES OF EXTREMITIES PROBABLY OF THE SAME GENERAL NATURE AS THOSE IN OTHER CASES, BUT UNPROVEN

(Cases 25 to 28, inclusive.)

CASE 25.—Donaldson,[20] 1903. Boy, aged 2½ years. Proptosis so extreme that right eye had become dislocated on eleven different occasions. Upper part

of forehead keel-shaped. Brachy and acrocephaly. "The great toes were broad and hallux varus was present on each side."

CASE 26.—Fletcher,[34] 1910. Boy, 14 years old. Oxycephalic skull. Exophthalmus and divergent squint. Superior maxilla shortened. Ear poorly developed, tragus rudimentary. Peculiar malformation of thumbs; first phalanx curved outward toward the radial side, the outward or radial side being shorter than the inner. (Report brief; photographs of hands and of front and lateral views of head; roentgenogram of head.)

CASE 27.—Hutchinson,[32] 1910. Girl, aged 4 years; ninth of ten children. Full term; rather difficult labor; mother had severe fright at sixth week of pregnancy. Oxycephalic head; circumference 17.5 inches. Exophthalmus with divergent eyes, left turned slightly down and out. Constant, irregular, chiefly lateral movements. Pupils react sluggishly to light; disks show well marked atrophy of secondary type with white lines along course of vessels; vision much impaired. Adenoid facies; high palate; narrow naso-pharynx; tubercle of atlas very prominent. Thumbs very broad; little fingers kinked like those of a Mongol. Viscera normal. Mental development backward. (Photograph of front view of head and hands shown: in Fletcher's report, Plate 36, photographs of front and lateral views of head of this case when 12 years of age are shown; also roentgenogram of head.)

CASE 28.—Fletcher, 1910. Man, aged 23 years. Head typically oxycephalic. Extreme proptosis; right eye more prominent than left; occasionally becoming dislocated forward in front of eyelids. Superior maxilla shortened from before backward. Hard palate, narrow, much arched. Elbows cannot be fully extended. Internal condyles unduly prominent. Some creaking in joints; head of both radius and ulna appears thickened. Unable to raise arms to horizontal; obvious creaking in both shoulder joints but no change found in the bones. (Well described; photographs of hands and arms, front and lateral views of head; roentgenograms of head and elbows.)

IV. CASES OF SCAPHOCEPHALY WITH SYMMETRICALLY DISTRIBUTED MALFORMATIONS OF THE EXTREMITIES

(Cases 29 and 30.)

CASE 29.—Küttner,[29] 1913. Boy, aged 1 year 2 months. Deformity of head fully developed at birth. Forehead extremely high and rises sheer; head very long. Region of anterior fontanel especially prominent; both fontanels appear to be closed. Sutures cannot be felt. Veins of scalp prominent. Root of nose depressed. Extreme degree of exophthalmos; eyeballs only partially covered by lids; optic neuritis present. Beneath occipital prominence a small flat "prolapse of brain" which pulsates and can be compressed. Extremities show "slight deformities of both thumbs and great toes." Marked convolutional atrophy shown in roentgenogram. Necropsy showed well marked internal hydrocephalus. (Description fair; photographs of head; roentgenogram of head; necropsy.)

CASE 30.—Authors. W. F.; first child, labor difficult, delivery instrumental. Child thought to be dead at birth. Deformity fully developed at birth. When seen at 4 months, head extremely high and long; parietal bones form a rounded arch; head acroscaphocephalic. Anterior fontanel very large, measuring 9.5 cm. in breadth by 10 cm. in length, tense and bulging. Posterior fontanel open, measuring 4.75 cm. by 0.5 cm. Wormian bone in anterior fontanel. Veins of scalp prominent. Mouth kept open; nasal obstruction. Marked proptosis. Palpebral apertures slant slightly outward and downward. Internal hydrocephalus of communicating type demonstrated by phenolsulphonephthalein test. Rudimentary tail present. Arms could not be completely extended at elbows. When seen at 3½ years, deformity of head and exophthalmos even more striking. Fontanels closed; marked bony prominence at the site of anterior fontanel. Child apparently sees and hears but is mentally retarded.

THE CALCIUM METABOLISM OF PREMATURE INFANTS *

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STOCKHOLM, SWEDEN

The calcium metabolism of premature infants has hitherto not been studied systematically. Such a study is, however, well justified by the fact that these infants are more liable to acquire rachitis than full-term babies. It is also a common experience that bone symptoms appear in the prematurely born at an early age, and that the condition more often takes a grave course than in other infants. It has been assumed that this tendency is caused by the absence of a congenital store of calcium, supposed to be present in full-term new-borns. About 85 per cent. of the body's calcium at birth is stored during the last two or three months of fetal life.[1] We do not know, however whether the large amount of calcium, thus retained, may in postnatal life really play the rôle of a depôt, the contents of which are available for the processes of growth. Be this as it may, a premature birth means that the body is exposed to postnatal life containing a proportionately very small amount of calcium. It has been surmised that this fact may be at least partially responsible for the prevalence of rachitis among the prematures.

If the calcium stored in the last months of fetal life, really is essential to the normal postnatal growth of the body, the premature birth would, it seems, lead to a state of calcium starvation. According to the present state of knowledge, however, rachitis and calcium starvation are not identical conditions. It might be possible that the assumed calcium starvation of the prematures would in some way make them more susceptible to rachitis. But there is also another possibility, namely, that some of the so-called rachitic symptoms of the prematures have nothing to do with rachitis, but are symptoms of simple osteoporosis.

One peculiarity of rachitis in prematures is the very early appearance of craniotabes. This symptom, rarely seen in full-term infants before the beginning of the fourth month, very often appears in prematures as early as the second month of life. (The craniotabes in prematures must not be confused with the general elastic flexibility of the flat bones of the skull in these infants; nor, of course, with con-

* From the "Sachs" Baby Hospital.
* Read in part before the First Scandinavian Pediatric Congress, Copenhagen, August, 1919.

1. Schloss: Die Pathogenese und Aetiologie der Rachitis sowie die Grundlagen ihrer Therapie, Ergebn. d. inn. Med. u. Kinderh. **15**:55, 1917.

genital bone defects). This early craniotabes of the prematures often develops to an extent rarely seen in infants born at full term. It is noteworthy that this excessive softening of the flat bones of the skull is often found in breastfed prematures in the best hygienic conditions, spared from infections and gaining rapidly in weight. The general condition of these infants, their often remarkable vitality, makes one doubt whether they are suffering from a rather severe disease; clinical observation as well as theoretical speculation therefore justifies the assumption of a nonrachitic origin of their symptoms in many cases.

The predisposition of prematures to acquire rachitis, however, can hardly be denied altogether. Among the cases of malignant rachitis in older infants, the cases with severe deformities of thorax and extremities, with general slackness of the muscles, there is a large percentage of prematures according to the experience gathered at this hospital.

TABLE 1.—SUMMARY OF THE MAIN RESULTS OF PREVIOUS WORKS ON CALCIUM METABOLISM OF BREAST-FED INFANTS

Author	Age in Mos.	Weight	Calcium Oxid			
			Total Intake	Intake per Kg.	Total Retention	Retention per Kg.
Peiser, G1*	2	3,720	0.279	0.075	0.048	0.013
Tobler-Noll†	2.5	4,000	0.2390	0.0598	0.0533	0.0133
Lindberg I‡	2.5	4,285	0.2572	0.0600	0.0562	0.0131
Lindberg II	2.5	4,370	0.2615	0.0598	0.0639	0.0146
Michel Perret§	3	4,725	0.377	0.080	0.149	0.032
Schabad¶	4	7,700	0.3636	0.0472	0.1815	0.0236
Blauberg#	5	6,740	0.272	0.0404	0.1754	0 0260
Howland and Stolte I‖	5	About 4,250	0.3337	0.0785	0.1053	0.0248
Howland and Stolte II	6	About 4,400	0.3307	0.0752	0.1107	0.0252

* Peiser: Beiträge zur Kenntnis des Stoffwechsels, besonders der Mineralien im Säuglingsalter, Jahrb. f. Kinderh. **81**: 437, 1915.

† Tobler and Noll: Zur kenntnis des Mineralstoffwechsels beim gesunden Brustkind, Monatschr. f. Kinderh. **9**: 210, 1910.

‡ Lingberg: Ueber den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Frauenmilchfett, Ztschr. f. Kinderh. **16**: 90, 1917.

§ Michel and Perret: Etude des échanges nutritifs azotés et mineraux chez un nourrison, Bull. Soc. d'obstét. de Par. 1899.

¶ Schabad: Zur Bedeutung des Kalkes in der Pathologie der Rachitis, Arch. f. Kinderh. **52**: 47, **53**: 380, **54**: 83, 1910.

Blauberg: Ueber den Mineralstoffwechsel beim natürlich ernährten Säugling, Ztschr. f. Biol. **40**: 36, 1900.

‖ Howland and Stolte: Die Bedeutung von Eiweisszulagen beim Säugling, Jahrb. f. Kinderh. **88**: 85, 1918.

The proportionately small amount of calcium in the body of the new-born premature may, as mentioned above, possibly lead to a state of calcium starvation in the course of postnatal growth. There are, however, in the postnatal growth of the premature often certain characteristic features which also might unfavorably influence the calcium metabolism. Although the difference in corporal development between the premature and the full term new-born may be very great,

there is in the healthy premature, when properly nourished and cared for, a great tendency to make good this difference. It is not unusual for such an infant to double its weight in three months and triple it in six months. The question now arises, whether the tissues formed by this rapid growth are of the same composition as in the more slowly growing bodies of normal infants. We know how the tissues formed in a rapid recovery from an acute or chronic nutritional disturbance, contain much water and are poor in salts. It may well be supposed that the same would be the case in the rapidly growing bodies of prematures. If this should be so, their bodies, already containing but a small amount of calcium at birth, would soon be really impoverished in respect to this substance.

The work of Klotz has been excluded, first because the infant practically did not gain in weight, and second because the calcium intake was abnormally low. One of Peiser's infants (infant Band) has also been excluded. This infant developed symptoms of syphilis some time after its metabolism had been studied and cannot, therefore, be considered a normal infant.

A study was made of infants born from four to ten weeks before full term. The cause of the premature birth was advanced pulmonary tuberculosis of the mother in three cases, nephritis and eclampsia in one case. In the cases of tuberculosis, the infants were separated from the mothers immediately after delivery. Symptoms of syphilis and tuberculosis were absent in all cases during the time of observation. The Wassermann test was negative. The infants were nourished from birth exclusively with breast milk given in bottles; they gained rapidly in weight during the months in which the experiments were carried out. A slight tendency to subnormal temperature was easily overcome. The stools were at times loose and frequent, both during the experiments and in the intervals. Such stools are often seen in normal babies fed with breast milk, and are nowadays not considered pathologic when, as in these cases, the infants are in all respects healthy, gaining in weight and showing a normal temperature.

The method used for collecting the stools and the urine was that described by Bendix-Finkelstein, slightly modified. Calcium was determined according to McCrudden.

The iron metabolism of these same infants was studied by Lichtenstein as a sequel to hematologic studies made on prematures.[2] The result of this study has not yet been published.

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2. Lichtenstein: Hämatologiska studier å för tidigt födda barn, Svenska Läk.-Sällsk. Handl. **43**:1533, 1917 (abstr. in Jahrb. f. Kinderh. **88**:387, 1918.

TABLE 2.—Study of the Calcium Metabolism of Four Prematurely Born Infants

Case	Date and Number of Experiment	Weight at Beginning and End of Experiment	CaO Intake, Gm. Daily	CaO Intake, per Kg., Gm. Daily	CaO in Feces, Gm. Daily	CaO in Urine, Gm. Daily	CaO, Total Output, Gm. Daily	Total Retention, Gm. Daily	Retention per Kg. Gm. Daily	Percentage of Intake Retained	Remarks
A. L.	12/10-12/19 I	1,930—2,140	0.1444	0.0710	0.0997	0.0107	0.1108	0.0340	0.0167	23.6	
Born 11/18	1/20- 1/29 II	2,830—3,150	0.2448	0.0819	0.2013	0.0051	0.2064	0.0384	0.0128	15.7	1/2: craniotabes
	3/20- 3/29 III	4,170—4,390	0.3097	0.0724	0.2041	0.0074	0.2115	0.0982	0.0229	34.7	3/6: extensive craniotabes
N. L.	1/ 8- 1/12 I	1,620—1,760	0.1339	0.0792	0.1130	0.0057	0.1187	0.0152	0.0090	11.4	1/13: craniotabes
Born 11/30	2/22- 3/ 3 II	2,620—2,870	0.1876	0.0683	0.1719	0.0076	0.1796	0.0081	0.0030	4.3	2/20: extensive craniotabes
	4/ 2- 4/ 6 III	3,670—3,840	0.2695	0.0718	0.2000	0.0080	0.2080	0.0615	0.0164	22.8	4/4: craniotabes progressing (the hole back of the skull)
	4/ 7- 4/ 9 IIIa	3,840—3,970	0.2976	0.0762	0.2239	0.0106	0.2345	0.0635	0.0165	21.3	Milk, 4/7–5/1, slightly enriched in calcium through addition of $CaCl_2$
	4/25- 5/ 1 IV	4,250—4,420	0.3092	0.0713	0.2024	0.0160	0.2184	0.0988	0.0228	29.4	5/27: extensive craniotabes; osteophytes on tubera frontal; slight rosary
S. P.	2/10- 2/19 I	1,770—1,970	0.1362	0.0728	0.1300	0.0054	0.1354	0.0008	0.0004	0.6	
Born 1/15	3/ 5- 3/14 II	2,210—2,440	0.1786	0.0768	0.1601	0.0053	0.1654	0.0132	0.0057	7.4	3/4: craniotabes; 4/3: craniotabes progressing
O.	6/ 6- 6/15 I	1,850—2,100	0.1637	0.0829	0.1490	0.0107	0.1597	0.0040	0.0020	2.4	
Born 5/17	6/17- 6/18 Ia	2,110—2,170	0.2789	0.1303	0.2075	0.0146	0.2221	0.0568	0.0265	20.4	Milk, 6/16–7/5, slightly enriched in calcium through addition of $CaCl_2$
	6/26- 7/ 5 II	2,290—2,560	0.2823	0.1164	0.2116	0.0193	0.2309	0.0514	0.0212	18.2	
	7/11- 7/20 III	2,690—3,020	0.2350	0.0823	0.1659	0.0031	0.1690	0.0660	0.0231	28.1	7/21: craniotabes

REPORT OF CASES

CASE 1.—A. L., born Nov. 18, 1918, four weeks before full term, with a birth weight of 1,930 gm. Admitted to the "Sachs" Baby Hospital November 27.

The calcium metabolism of this infant was studied in the second, third and fifth month (ten day periods). The calcium retentions found per kilogram of body weight were of the same magnitude as those found by other investigators in full term infants. Craniotabes appeared shortly after the end of the first period and progressed rapidly in the following months.

CASE 2.—N. L., born Nov. 30, 1918, from eight to ten weeks before full term. Birth weight, 1,550 gm. Admitted December 13.

The calcium retentions found in the second and third months (two ten day periods) were very low. Craniotabes appeared in the second month and progressed rapidly, until in the fourth month the whole back of the skull was softened. Somewhat later there also developed osteophytes on the frontal bones and rosary. At this time a five day period showed a tolerable calcium retention. Calcium chlorid was now added to the milk (about 0.03 gm. daily); the retention remained the same (period III a, three days). The administration of calcium chlorid was continued, and two weeks afterward the retention was decidedly better (period IV, seven days), whether because of the artificially increased intake it is impossible to decide.

This infant spent thirty-five days out of 124 on the metabolism frame. The calcium retention was never found to be negative, although pronounced pathologic bone symptoms appeared and progressed during this time.

CASE 3.—S. P., born Jan. 15, 1919, from six to eight weeks before full term with a birth weight of 1,600 gm. Admitted January 17.

The calcium metabolism was studied in the first and second month of life (ten day periods). The retentions were very low. Craniotabes appeared in the second month.

CASE 4.—O., born May 17, 1919, one month before full term. Birth weight 1,670 gm. Admitted May 24.

The first experiment with this infant was made when it was 3 weeks old (a ten day period). The calcium retention was found to be very low (0.0020 gm. per kilogram). When this period was finished, calcium chlorid was added to the milk (about 0.1 gm. daily). Twenty-four hours afterward a second period (I a, two days) was begun. The retention was now more than tenfold (0.0265 gm. per kilogram). The administration of calcium chlorid was continued. Eight days after the second period a third period (II, ten days) showed about the same retention (0.0212 gm. per kilogram). Calcium chlorid was now left out. In spite of this, the retention found in the last period was not altered; a fact, the probable explanation of which will appear from the discussion of the experiments. Craniotabes appeared in this infant shortly after the end of the experiments.

DISCUSSION

Three infants out of four studied had very low calcium retentions during the first months of life. This might possibly be ascribed to rachitis, as in all the infants craniotabes appeared in the second month. This assumption, however, is not in harmony with the fact that although the craniotabes in those cases which were followed further made progress in the subsequent months, the retentions increased to amounts as large as those found in normal infants. I wish further to call attention to the relatively normal retention of the infant A. L., period I, immediately before the craniotabes was clinically noted; the

appearance of rachitic symptoms is generally believed to be preceded by low or negative calcium retentions. Lastly, the calcium metabolism in progressive rachitis cannot, as far as we know, be influenced by the administration of calcium, as was done in the case of the infant O.

There are, then, several discrepancies between these prematures and rachitic infants in respect to their calcium metabolism, its relations to clinical symptoms and therapeutic measures—discrepancies which justify the proposal of another explanation of their low retentions.

TABLE 3.—TOTAL INTAKES COMPARED WITH THE RETENTIONS PER KILOGRAM OF BODY WEIGHT

Case	Period	Total Intake in Mg.	Retention per Kg. of Bodyweight	Case	Period	Total Intake in Mg.	Retention per Kg. of Bodyweight
N. L.	I	133.9	9.0	A. L.	II	244.8	12.8
S. P.	I	136.2	0.4	N. L.	III	269.5	16.4
A. L.	I	144.4	16.7	O.	Ia	278.9	26.5
O.	I	163.7	2.0	O.	II	282.3	21.2
S. P.	II	178.6	5.7	N. L.	IIIa	297.6	16.5
N. L.	II	187.6	3.0	N. L.	IV	309.2	22.8
O.	III	235.0	23.1	A. L.	III	309.7	22.9

In Table 3 the rather remarkable fact is demonstrated that in those periods where the intakes exceed 200 mg., the retentions are sufficient (i. e., as large as in normal infants), while in the periods where the intakes are lower than this amount, there is sufficient retention only in one case. It is tempting to draw the conclusion that the intake must exceed a minimum of about 200 mg. if sufficient retentions are to be attained. The total calcium excretion cannot, it seems, be pressed below a certain level. The calcium is excreted mainly in the stools. The daily amount of feces excreted by prematures is very large, a fact which may be explained by the low fat absorption found in prematures by Rubner and Langstein. The daily values for the total solids [3] in the stools are consequently high, higher than in normal infants, although the quantities of milk taken by the prematures are very small. The calcium percentages of the total solids were, in my experiments, found to be lower than in normal infants, not, however, sufficiently lowered to counterbalance the excess in total solids and the small intakes. To balance these factors, exceedingly low calcium percentages would have been necessary. It might be conceivable that for reasons unknown to us, such exceedingly low percentages cannot be attained under ordinary conditions.

Lindberg's experiment [4] where an infant was alternately fed with ordinary breast milk and breast milk enriched with fat (breast milk

3. As fat analyses have not been made (because of lack of the necessary reagents) the following discussion is based on the values for total solids.

4. Loc. cit., Table 1.

fat used), demonstrates that a high fat intake may in the breast fed infant lead to temporary losses of calcium. The increased fat intake was followed by an increased fat excretion, i. e., an increase of the daily amount of total solids in the stools; the dry weight of the stools increased 27 per cent. The calcium percentage, however, fell only 15 per cent., i. e., the increase in total solids was not balanced. Lindberg's experiment with high fat intake lasted only six days. During this time, the feces had the same characteristics as the feces of prematures: rich in fat and consequently in total solids; calcium percentage somewhat low, but not sufficiently lowered to bring about a good calcium retention. In the normal infant the cause was an excess of fat intake; if the experiment had been continued for a longer period, it is highly probable that some regulating mechanism would have been called into play and a normal calcium metabolism re-established. In the premature, the constantly low fat absorption suggests an insufficiency of the digestive mechanism. It is not inconceivable that this supposed insufficiency is also responsible for the low calcium retentions.

Holt and his co-workers [5] in their work on calcium and fat metabolism in bottle fed infants found no constant relation between calcium and fat excretion. The work of Lindberg demonstrates that in a breast fed infant with abnormally high fat intake such a relation may exist. Perhaps the experiments here reported may be interpreted thus: that in breast fed infants the same relation is found when the fat absorption is low.

In this discussion, an attempt has been made to find a plausible nonrachitic cause for the low calcium retention found in prematures. The argument would be strengthened if it could be demonstrated that these low retentions may be increased not only by a higher calcium intake but also by a lower fat intake.[6] At present, however, the available facts are neither numerous nor complete enough to justify the drawing of definite conclusions.

I wish to thank Dr. A. Lichtenstein for taking the initiative in this work, and for his valuable advice and criticism.

5. Holt, Courtney and Fales: Calcium Metabolism of Infants and Young Children, and the Relation of Calcium to Fat Excretion in the Stools, Am. J. Dis. Child. **19**:97 (Feb.) 1920.

6. In the discussion of this paper Dr. A. Ylppö announced that he had recently begun feeding prematures with centrifugated breast milk. The result of this experiment has not yet been published.

OBSERVATIONS ON TUMORS OF THE KIDNEY REGION IN CHILDREN*

LANGLEY PORTER AND WILLIAM E. CARTER
SAN FRANCISCO

Tumors in the kidney region of children may be either benign or malignant. Cystic enlargements of the kidneys are fairly common. The benign growths may appear as adenomas, angiomas, lipomas or fibromas. Cysts occur as congenital cystic kidney; acquired as results of hydronephrosis or of pyonephrosis, or as hydatid cysts. Reports of cases of congenital hydronephrosis without malignancy are included in this study.

Malignant tumors of the kidney are grouped variously. An accepted classification has yet to be made. In general, these cases fall into the group of carcinomas, sarcomas and hypernephromas.

The malignant tumors of the kidney region are the kind which usually occur in young patients. The greatest number of cases occur between the ages of 6 months and 6 years. Of all malignant growths affecting children, those affecting the kidneys appear to be second in number. D'Espine and Piso constructed a table which sets forth in order of frequency the structures involved in cases of malignant tumors occurring in children. Three hundred and ninety-three cases were analyzed. The eye and orbital structures were involved in 52 per cent.; the kidney in 20 per cent.; the bone in 17 per cent.; the brain in 5 per cent. and the abdomen and pelvis in 4 per cent.

Albarran and Imbert tabulated 600 cases of kidney tumors occurring at all ages. Twenty-two of these were in children. Forty per cent. were epitheliomas; 20 per cent. were hypernephromas, and 30 per cent. were mixed tumors. Other writers have reported equally significant figures.

In looking over the case records of the University of California Hospital, Stanford University Hospital, San Francisco Children's Hospital and our own case records for the last five years, we have been able to find eleven cases. They fall into the following groups: Sarcoma, 4 cases; carcinoma, 3 cases; malignant kidney, unclassified, 2 cases, and hydronephrosis, 2 cases.

All the patients were less than 7 years of age.

Sarcomas have been found in the kidney as early as the sixth month of fetal life. Many references are made in the literature to two cases reported by Paul of Liverpool in which the tumor was

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discovered during the examination of the kidneys of stillborn infants. It is probable that more cases would be reported if routine histologic examination of stillborn babies were the rule.

One case coming under our observation was of unusual interest. The tumor was found in a child at term. The mass was so large that it obstructed labor. While the literature contains several reports of cases of small malignant kidney growths found at birth, we have been unable to find any reference to the antenatal development of a tumor of such dimensions.

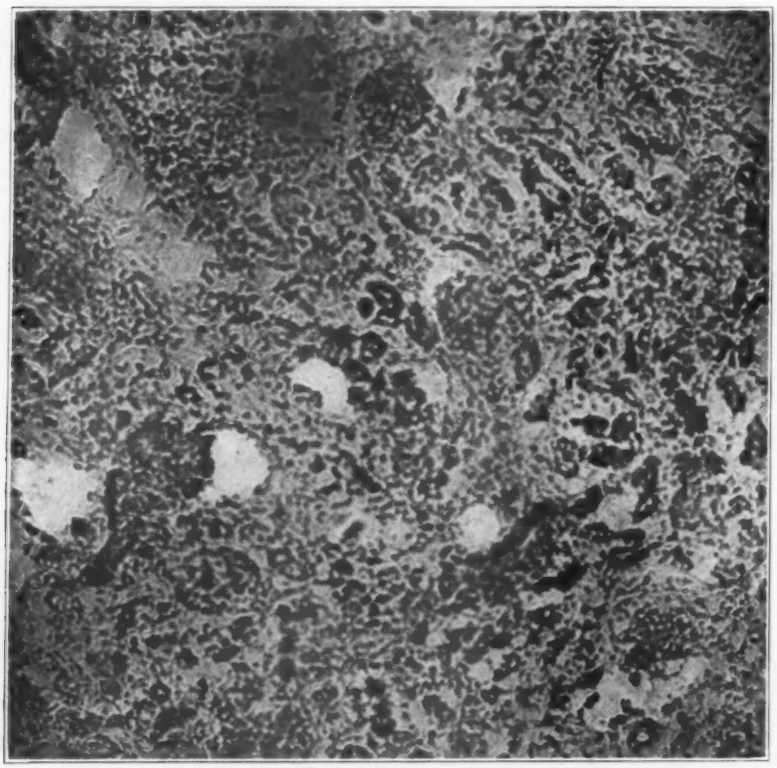

Fig. 1.—Microscopic section of round cell sarcoma of kidney.

REPORT OF CASE

Mrs. P., aged 35; Italian; first baby at 16 years. Has had five pregnancies, four with normal course and delivery. Of these children, one died at 4 years of appendicitis; three are living and well.

There is a history of a severe and protracted cold, extending over the first four months of pregnancy. Emesis occurred daily from the fourth to the sixth month. Other than these two features, there was nothing unusual in the course.

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1. Called to our attention by Dr. A. S. Musante and Dr. Thomas Maher.

Fig. 2.—Sarcoma of kidney.

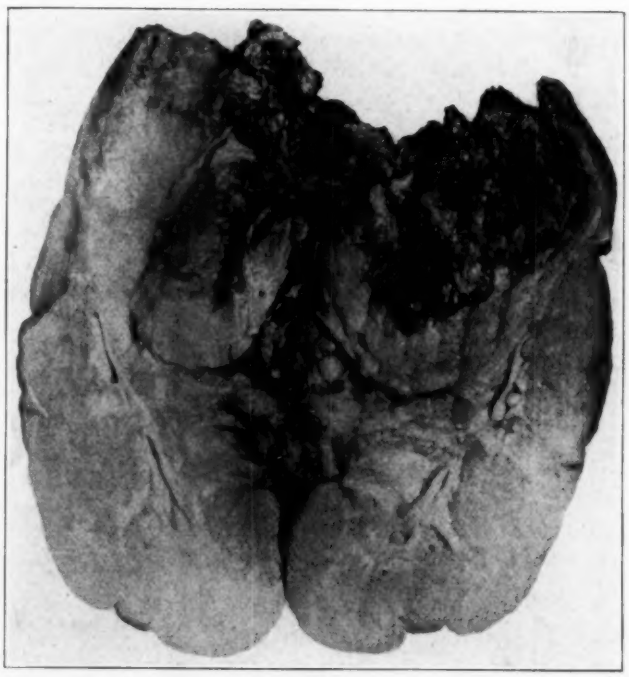

Fig. 3.—Carcinoma of kidney; cross section.

Fig. 4.—Carcinoma of kidney; cross section.

Fig. 5.—Case of hydronephrosis, result of congenital narrowing of ureter; authors' case.

Labor: Beginning at 5 p. m., the patient had pain in her back and lower abdomen. At 9 p. m. she had a sudden rupture of the membranes with a discharge of black fluid. At 11 p. m. the head, shoulders and arms of the child were delivered, but the remainder of the body could not be brought down. The attending physician called a consultant. The patient was anesthetized; an incision was made in the body of the dead fetus just below the ensiform cartilage; the hand was introduced and a large amount of soft, friable tissue was removed from the abdominal cavity of the infant. This manipulation reduced the tumor mass sufficiently for the body to pass through the birth canal.

In size the mass appeared to be one and a half to two times that of the fetal head. The part of the tumor which was removed was of grayish color; a pinkish framework ran through it and it was semisolid in consistency.

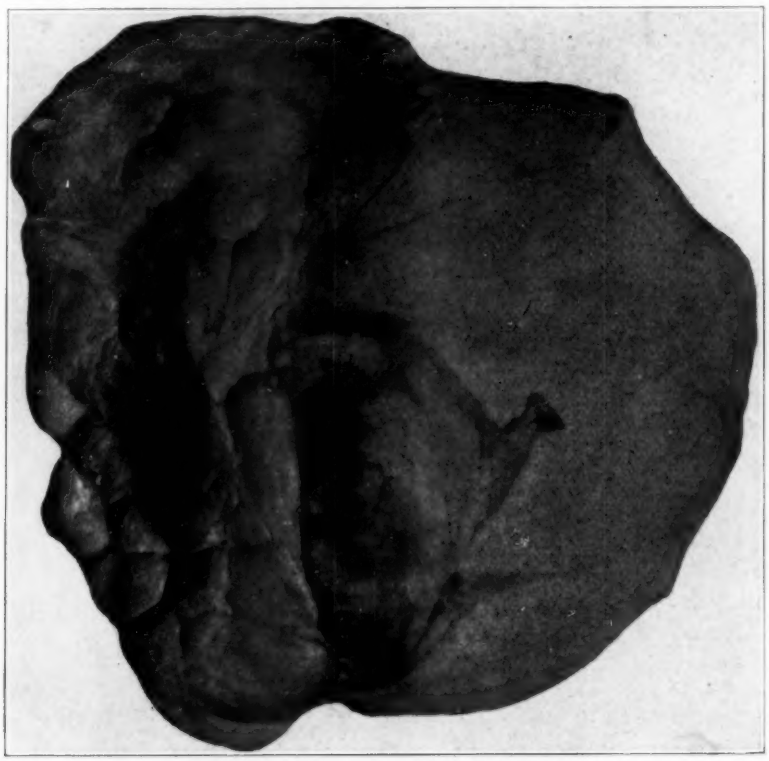

Fig. 6.—Kidney from authors' case.

The pathologist's report showed the tissue to be a round-cell sarcoma. The presence of glomeruli in the section indicates the kidney origin of the tumor (Fig. 1).

DISCUSSION OF CLINICAL HISTORY AND OF THIS TYPE OF CASE

True sarcomas are usually irregular in form, and they are contained within the fibrous capsule of the kidney. Their color varies from that of the meat of a white fish to a bright red. They may attain great size; one reporter saw removed from a child a kidney tumor which weighed more than the postoperative weight of the

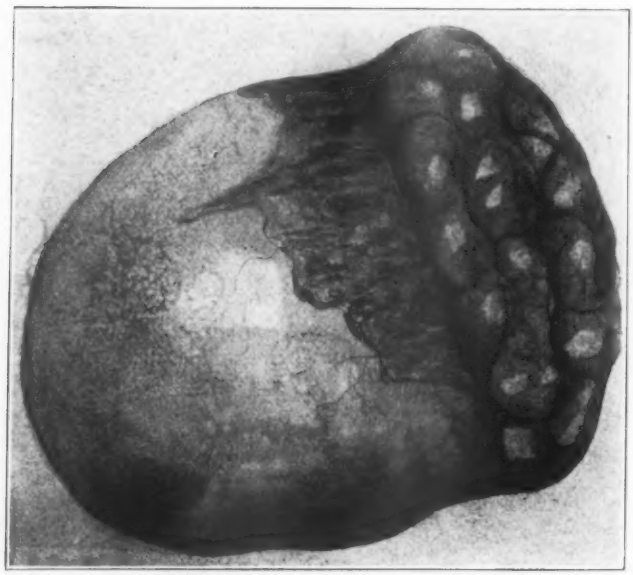

Fig. 7.—Another view of kidney from authors' case.

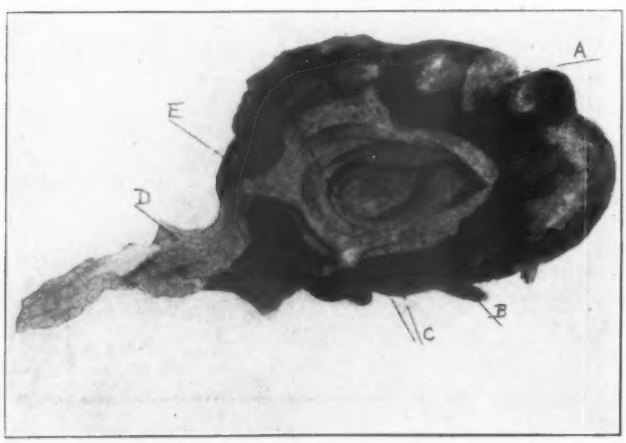

Fig. 8.—Photomicrograph of a malignant kidney producing dystocia?

patient from whom it was taken. Several cases are reported in which the tumor is said to have weighed from ⅓ to ½ of the child's post-operative weight. On cut section, these tumors exhibit any degree of hardness, from woody to scirrhus. Occasionally there will be found scattered throughout the kidney structure cysts which represent late hemorrhages or mucinous degeneration. Such cysts may lead to errors in diagnosis as the fluctuation may be mistaken for that of a true cyst or a hydronephrosis. Metastases sometimes occur in the lymph nodes, liver, peritoneum, pancreas and bladder.

The symptoms and signs of malignancy of the kidney are fairly uniform, and the diagnosis can usually be made before the child is cachectic. Early in the course there is commonly a period of anorexia, malaise and vomiting. The loss of weight is progressive. Pain is frequently an early symptom. The temperature ranges from normal or subnormal during the early stages to 104 or 105 F. during the later days.

The physical signs consist of the early appearance of a fullness at the costo-vertebral angle of the affected side. Later, a tumor mass may be revealed by palpation and percussion. In many cases, this mass fills a large part of the abdomen. Ballottement, gently applied at the costo-vertebral space, is of paramount importance as a diagnostic measure. The firm but gentle, intermittent pressure of the finger applied here, usually senses enlargements in the kidney or about it.

If the urine is watched, it will be found that intermittent hematuria is not infrequent. Pus cells and casts are often found. The blood changes are seldom more than those of a secondary anemia.

A roentgenogram is of particular value in arriving at a diagnosis. A good anterior projection will occasionally show the tumor mass clearly outlined. Injecting the colon with oxygen or air will often assist in defining the shadow of the tumor. The more recent advances in roentgenography in which oxygen or carbon dioxid is injected into the peritoneal cavity may prove to be of considerable value.

Renal malignancy may be mistaken for a tuberculous peritonitis, but in the latter condition there is usually felt a sausage-shaped mass extending diagonally across the abdomen. This tumefaction corresponds to the free margain of the mesentery. Fullness at the costo-vertebral angle, so characteristic of kidney tumor, is rarely found in tuberculous peritonitis.

The disease runs a rapid course. Guillet says that children so affected die on an average within a year. Roberts and Taylor say seven months. Albarran and Imbert state that of twenty children who were not operated on, fourteen were dead within six months after the

discovery of the tumor and only one child survived three years (Figs. 2, 3 and 4).

Malignant kidney tumors may be confounded with hydronephrotic. The diagnosis is especially difficult when such a tumor degenerates, acquires fluid and on physical examination is found to fluctuate.

Hydronephrosis, Figures 5, 6, 7, 8, is produced by obstruction of the ureters and a damming back of the urine. This obstruction may be due to pressure from without or to a stenosis or an atresia of the ureter. A solid tumor of the kidney, by virtue of its size, may press on the ureter of the opposite kidney and so give rise to a hydronephrosis. Pressure on a ureter from impingement of an anomalous accessory renal artery may lead to retention of urine in the kidney. Occasionally a concretion lodged in the kidney pelvis or in the ureter may be the cause of the blocking. A congenital narrowing of the ureter may be the etiologic factor, as in one of our cases (Fig. 8).

SUMMARY

1. Malignant kidney tumors may develop in the child in utero and become of sufficient size to obstruct labor.

2. Ballottement, applied to the costo-vertebral space, is of value in the diagnosis of tumors in the kidney region, and this maneuver should be routinely employed in the examination of children.

STUDIES IN METABOLISM. II. THE METABOLISM OF A VERY OBESE CHILD WITH A SMALL SELLA TURCICA (TYPUS FRÖLICH ?)

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A boy, W. N., aged 2 years and 9 months, entered the Children's Medical Service at the Massachusetts General Hospital June 9, 1919. He was a full term baby, and for the first nine months was fed on drawn breast milk because his mouth would not open wide enough to permit him to nurse. Up to the end of the first year he was a very thin and poorly developed infant. He then commenced to gain rapidly in weight and has continued to do so up to the present time. His weight on entering the hospital was 24.82 kilos, (54 pounds, 9½ ounces). His mental development was that of a 10 months old infant. He recognized his family, but did not talk or feed himself, and was unable to stand alone. He was said to sleep well, to be happy and contented, and to have a good digestion.

The physical examination showed an extremely obese child with a sluggish mentality and a hoarse voice. His skin was like satin and the hair slightly coarse. The features and all parts of the body were large, except the penis and testicles, which were smaller than normal. There were great rolls of fat all over the body. The physical examination was otherwise normal. His body measurements were as follows:

Naked body weight	24.82 kilos	54 lbs. 9½ ozs.
Height	94 cm.	36⅞ inches
Circumference of head	49.4 cm.	19⅜ inches
Circumference of chest	75.5 cm.	29⅝ inches
Circumference of abdomen	74.4 cm.	29¼ inches
Circumference of hips	73.0 cm.	28⅝ inches
Length of arm	41.0 cm.	16⅛ inches
Length of leg	46.7 cm.	18¼ inches

Body surface (measured by DuBois formula) = 0.879 square meters.

A two hour pulse, respiration, and temperature chart showed that the pulse and respiration responded to muscular activity in a normal manner. The rectal temperature tended to be slightly elevated, between 99 and 100 F. The patient perspired easily and seemed nervous and fussy. The average daily number of calories in the food for three weeks was 895, on which he gained slightly in weight. The average caloric requirement for his age is about 1,200 calories. When the food was cut down to between 700 and 800 calories he commenced to lose weight.

June 10 the administration of 10 grains of whole pituitary gland daily was commenced and continued for a period of five weeks, during which time he had lost eight pounds and had improved both mentally and physically. The pituitary gland was then omitted for four days and he regained some weight previously lost, but lost it when the pituitary gland was again commenced. Toward the end of his stay in the hospital he was trying to walk and commenced to talk.

Fig. 1.—Excessive obesity, tapering fingers and stupid facial expression.

A study of the basal metabolism of this child was made in order to determine how much his metabolism varied from the normal found by Benedict and myself.[1] Figures of the basal metabolism represent, of course, the minimum metabolism of a child which is absolutely

1. Talbot: Metabolism and Growth from Birth to Puberty, to be published later as Carnegie Institution of Washington Publication, No. 302.

quiet, without food in the stomach, and in very young children who are usually asleep. These figures are the lowest figures obtainable consistent with life and leave out of consideration the energy required for activity and growth and the energy lost in the excreta. The only way by which comparisons of basal metabolism can be made is when the child is under basal conditions, that is, conditions in which all factors which increase the metabolism above the basal, are excluded.

His metabolism determined before treatment was commenced was as follows:

TABLE 1.—METABOLISM OF W. N. BEFORE TREATMENT

June 9, 1919	CO_2 Produced, Calculated to Hour Basis	Heat Produced per 24 Hours				Average Pulse Rate	Relative Activity
		Total	Per Kilo	Per Sq. Meter			
				Liss-auer	DuBois		
	Gm.	Cals.	Cals.	Cals.	Cals.		
Maximum	....	919	37	1,049	1,046	130	III. Playing with hands and tubing
Minimum	7.84	626	..	...	...	83	I. Asleep
	8.46	675	..	...	...	80	I. Asleep
	7.46	595	24	679	677	82	I. Asleep
Average minimum	....	632	24	679	677	81	I.

His total basal metabolism was found to be the same as that of boys of the same age, that is 631 calories. He was given food containing 895 calories, on which he continued to gain in weight. This would have been surprising if it were not for the fact that he was sitting or lying quietly all day and showed very little desire to move. This left 264 calories in the food which were not used up in the basal metabolism. From this must be subtracted 10 per cent. of the total intake, or, roughly, 90 calories, lost in the excreta, leaving 174 calories to be divided between muscular activity and growth. The gain in weight could only come if the child was very quiet.

When his total metabolism was compared with boys of the same weight, it was found to be 37 per cent. below the average. The heat production per kilogram of body weight when compared to that of boys of the same age was found to be 56 per cent. below the average, and when compared to that of normal boys of the same weight, it was 40 per cent. below the average. This is a very low metabolism and is comparable with that found in J. J. M. previously reported by me.[2]

2. Talbot: The Energy Metabolism of an Infant with Congenital Absence of the Cerebral Hemispheres, Arch. Pediat. **32**:452, 1915.

J. J. M. was found to have congenital absence of both cerebral hemispheres and his body was very fat with little muscle. In both of these children the amount of fat, which is inactive so far as the energy metabolism is concerned, was relatively very great as compared to the active tissues such as muscle and organs. The very low metabolism, even when compared to body surface, could, therefore, be due to the obesity of the child.

Fig. 2.—Rear view of same patient as shown in Figure 1.

Table 2 sets forth certain points of similarity in three cases. The metabolism per unit of body weight and per square meter of body surface is lower than the average for the same age and sex.

Although the findings in the case of W. N. can be explained in part by the obesity and the absence of muscular tissue, they are out of proportion to what has been found in normal fat children. The question naturally arises whether some other factor may not also play a part in causing the low metabolism.

TABLE 2.—Points of Similarity in Three Cases

Case	Age	Weight	Height	Total Heat			Remarks
				Per 24 Hrs.	Per Kilo	Per Sq. M. Body Surface	
		Kg.	Cm.	Cals.	Cals.	Cals.	
J. J. M.	8 mo.	8.43	73.5	245	27.0	574	Infant without a brain
C. G.	3 yr. 8 mo.	11.83	85.0	479	40.5	898	Cret:n [3]
W. N.	2 yr. 9 mo.	24.82	94.0	632	24.0	677	

If the metabolism per square meter of body surface in W. N. is now studied and compared with that of normal boys of his own weight and age, a striking variance from the average will be found. When compared to boys of the same age it is 41 per cent. below normal, and of boys of the same weight, 32 per cent. below normal.

Fig. 3.—Roentgenogram of skull showing constriction of neck of sella turcica and hypertrophy of posterior clinoid process.

Means [4] has shown that simple obesity in adults, as expressed in terms of surface area, does not alter the basal metabolism. In children and infants, on the other hand, there is a tendency for the fatter individuals to have a lower metabolism both per kilo of body weight and per square meter of body surface than for children of the average weight. One might speculate on the importance of observations with such marked deviation from the normal basal metabolism as was found in this case.

3. Talbot: Am. J. Dis. Child. **12**:145, 1916.
4. Means: The Basal Metabolism in Obesity, Arch. Int. Med. **17**:704, 1916.

SUMMARY

W. N. showed a very low metabolism from every point of view as compared with normal children of the same age, except the total basal metabolism. When he did not receive the pituitary extract he gained in weight and presumably put on fat very rapidly even on a diet containing relatively few calories. After pituitary extract was supplied he lost weight and commenced to develop mentally. It is to be hoped that the metabolism of similar cases will be studied in the future and thus throw light on such obscure conditions as this child presents.

THE FATE OF SUBCUTANEOUSLY INJECTED RED BLOOD CELLS *

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PART I.

Modern methods of intravenous transfusion are so satisfactory that today the question of using an extravascular route arises in infants only. A study of the older writings shows that at different times and places both the subcutaneous and intraperitoneal routes were employed and in the opinions of the reporters usually with success. My interest in the subject arose from observations made on two patients who were injected subcutaneously after unsuccessful attempts at intravenous transfusion. One of the patients, whose cells were never greatly diminished, showed a decided rise in hemoglobin, and the second patient showed a marked rise in both hemoglobin and cells. Unfortunately for the experiment, however, both patients were given iron. I then purposely employed the subcutaneous rather than the intravenous route in three patients who received no drug. The blood was citrated. With the exception of Ann F., who was given blood from her mother, all patients' blood groups were determined and a blood given whose corpuscles would not be agglutinated by the recipient's serum.

Two were University Hospital patients and on them was made the study which is reported in the second portion of this paper. The pertinent clinical data from all five cases is presented in Table 1. The Dare hemoglobinometer was used in the three private cases and the Fleischel-Miescher instrument was used in the University Hospital cases. The hemoglobin and red blood cell estimations were made in the private cases by a trained laboratory technician, and in the University Hospital cases by Dr. Ott, the resident in pediatrics. The results are as reliable as one can expect from the method employed.

It is apparent that the injection was usually followed by an increased hemoglobin percentage.

PART II.

Karst,[1] in 1873, noted that blood injected subcutaneously caused a transitory swelling only—and hastily concluded that it was absorbed

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* Read before the American Pediatric Society, June 2, 1920.

1. Karst: Injectionen von defibriniertem Blute ins Unterhautbindegewebe, Berl. klin. Wchnschr. **10**:587, 1873.

into the circulation. Later workers, Bareggi,[2] Orth,[3] Müller[4] and others, showed that after such injections, the more remote as well as the neighboring lymph glands became swollen and engorged with blood cells, and that within an hour thereafter large numbers of red blood cells were to be found in the thoracic duct.

As bearing on this point of the absorption into the circulation of extravascularly introduced blood, it is to be noted that Hayem[6] after peritoneal injection of dogs' blood into goats recovered dogs' corpuscles from the circulating blood of the latter.

Recently Scott[6] and Hanson injected stained foreign corpuscles subcutaneously and later found them in the recipient's circulation. We can accept as proven the thesis that subcutaneously injected red blood cells are qualitatively capable of reaching the recipient's circulation.

How many cells do so?

It occurred to me that the method devised by Ashby[7] for determining the length of life of the transfused corpuscle offered a way to the solution of the problem.

The method was applied in the two University Hospital cases, Nos. 16706 and 16895. The bloods of these two patients were in Groups III and II. Before receiving the blood injection, their own blood cells were counted, Group II serum being used as a diluent in the hemocytometer in the first case, and Group III serum in the second. Counts of the unagglutinated cells were made on the day preceding the injection and on the first and fifth days thereafter.

Ashby's technic was followed exactly—and all counts were made in duplicate and accompanied by control counts to check the continued agglutinative capacity of the serum.

Table 2 presents the results. In the last column is shown the estimated number of unagglutinatted cells per cubic millimeter which would have been present had all the injected blood cells reached the recipient's circulation. It is evident that this number was never approached and that even five days after the injection the number of unagglutinatted cells was not definitely increased.

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2. Bareggi: Arch. per le scienze med. **7**, No. 4, quoted by Wm. Hunter, op. cit.
3. Orth: Beitrag Zur Kenntniss des Verhaltens der Lympdrüesen bei der Resorption von Blut-extravasaten, Virch. Arch. **56**:269, 1872.
4. Müeller: Untersuchungen üeber das Verhalten der Lymphdrüesen bei der Resorption von Blut-extravasaten, quoted by Wm. Hunter, op. cit. 1879.
5. Hayem: De la transfusion peritoneale. Compt. rend. **88**:749, 1884.
6. Prof. F H. Scott, personal communication.
7. Ashby: The Determination of the length of life of transfused blood corpuscles in man, J. Exper. Med. **29**:267, 1919.

TABLE 1.—CLINICAL DATA

Case	Diagnosis	Age	Amount Blood Injected, C.c.	Body Weights and Red Blood Cell and Hemoglobin Estimations																
				Before Injection			1 Week After Injection			2 Weeks After Injection			3 Weeks After Injection			4 Weeks After Injection					
				Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.	Weight, Gm.	Red Blood Cells	Hemoglobin, per Cent.			
Marj. G. Received iron	Rickets, anemia	10 mos.	75	6,750	4,712,000	27	.....	.....	....	6,750	.....	47	.....	.....	....	6,825	.....	66			
Paul H. Received iron	Celiac disease	2½ yrs.	100	7,900	2,776,000	43	9,000	3,900,000	50	.....	.....	....	9,000	3,984,000	6 8						
Ann F.	Anemia	8 mos.	60	6,250	4,630,000	25	.....	.....	....	.....	.....	....	.....	.....	....	6,775	4,200,000	35			
Univ. Hosp. No. 16706	Purpura hemorrhagica	7 yrs.	130	26,000	4,750,000	75	.....	.....	69	.....	4,270,000	73									
Univ. Hosp. No. 16895	Hemophilia	2 yrs.	100	13,400	5,200,000	47	.....	.....	60	.....	4,420,000	70									

Recently, after consultation with me, Giffin and Ashby, at the Mayo Clinic, carried out a similar experiment on an adult who had pernicious anemia. Dr. Ashby has sent me the results with permission to publish them. The patient received 250 c.c. of blood subcutaneously. His average initial nonagglutination count was 50,000 and the post-injection count was 97,350. Ashby estimates that the increased number of cells should in this case equal 250,000 and states that if any of the blood got into the circulation it was only a fraction.

This is entirely different from Ashby's results on intravenously transfused individuals as reported in her work on the length of life of the transfused corpuscle. For example, the initial nonagglutination count in one patient, an infant weighing 20.5 pounds, was 54,400. He was given 220 c.c. of blood, and his unagglutinated cells rose to 1,175,000.

TABLE 2.—COUNTS OF UNAGGLUTINATED RED BLOOD CELLS BEFORE AND AFTER INJECTIONS OF GROUP IV BLOOD, THE COUNTING MEDIA BEING AGGLUTINATIVE TO THE RECIPIENT'S OWN CELLS BUT NOT TO THOSE GIVEN HIM

Case Number	Weight, Kg.	Recipient's Own Blood Group	Serum Used as Counting Medium	Amount Blood Injected, C.c.	Numbers of Unagglutinated Corpuscles per C.c.			
					Day Preceding Injection	Day After Injection	Five Days After Injection	Theoretical Number if All Injected Blood Had Been Absorbed
16706	27.0	III	II	130	48,400	50,550	100,350	350,000
16895	13.4	II	III	100	189,750	132,825	162,450	780,000

Subcutaneous injection of blood is usually followed by a rise in hemoglobin percentage: but only a small fraction of the cells so injected reach the circulation of the recipient.[8]

8. The following references may also be consulted:
Hirsch: Ueber subcutane Blut-transfusion nach der von Ziemessenschen Methode, Berl. klin. Wchnschr. **25**:790, 1888.
von Ziemssen: Ueber subcutane Blut-injection und ueber eine neue Methode der intravenösen Transfusion, Verhandl. Inner. Med. Elfter Congress 166-175, 1892.
von Ziemessen: Subcutaneous Blood Injections, J. A. M. A. **9**:35 (July 9), 68 (July 16) 1887.
Sicard: Homohémothérapie sous-cutanée, LaPresse méd., **33**:304, 1918.
Hunter, Wm.: Intraperitoneal Blood transfusion and the Fate of absorbed blood, J. Anat. & Physiol. **21**:138, 264, 450, 1886.

PNEUMOCOCCUS PERITONITIS IN INFANCY AND EARLY CHILDHOOD

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Pneumococcus peritonitis is a rather rare disease among infants and young children. The great majority of the patients in the Babies' Hospital are under 2 years of age, although those up to 4 years are admitted. In the last thirteen years there have been treated 171 cases of general peritonitis of which nine have been proved bacteriologically to be of pneumococcus origin.

This form of peritonitis has been well described by Jensen,[1] Brunn,[2] Annard and Bowen,[3] Rischbieth,[4] Cameron [5] and Abt.[6] It is not the purpose of this paper to duplicate their work, but to point out some of the peculiar features which this disease presents during very early life.

The pathology of the peritoneal inflammation is a purulent fibrinoplastic exudate which involves the whole peritoneal cavity. If the patient lives, adhesions form in the exudate which limit the process, finally causing a localized abscess. In this it differs from other forms of purulent peritonitis seen in children. The source of infection of the peritoneum is undoubtedly through the blood stream. Where the blood has become infected has been a matter of controversy. Barling concludes that the lungs are the primary focus in most cases. Brunn considers the middle ear as the chief portal of entry for the pneumococcus. Annard and Bowen, Jensen and Cameron think the intestines are most often the source of the infection. From a study of our cases it appears that in young children the source is most frequently the lungs. In seven of our nine cases distinct pulmonary symptoms preceded the peritoneal inflammation. Two were apparently idiopathic. No source of the infection of the peritoneum in these two latter cases could be found either in the lungs or elsewhere in the body. It is probable that the pneumococcus usually enters through the respiratory tract, and that it may enter the blood stream without localizing in the lungs. This probably explains the peritonitises apparently idiopathic in origin. There is no evidence in the cases reported

1. Jensen, J.: Lanngenbeck's Arch. f. klin. Chir. **69**: 1903.
2. Brunn, M. von: Beitr. z. klin. Chir. **39**:57, 1903.
3. Annard, W. F., and Bowen, W. H.: Lancet **1**:1951, 1906
4. Rischbieth, H.: Quart. J. Med. **4**: 1911.
5. Cameron, H. C.: Brit. J. Child. Dis. **9**:288, 1902.
6. Abt, I. A.: New York M. J. **105**:769 (April 28) 1917.

here that the middle ear or the intestines are the sources of infection with the pneumococcus.

The following nine cases show that clinically two types of the disease are met with: (1) Those which are clearly secondary to a pneumonia or an empyema and (2) those which are apparently primary. The onset of the first may be unattended by any definited symptoms or these symptoms may be so slight as to be easily overlooked, and nothing is apparent until the peritonitis becomes localized and abdominal distention is present. The onset of the second group is characterized by symptoms so acute as to immediately overwhelm the patient.

REPORT OF CASES

PNEUMOCOCCUS PERITONITIS SECONDARY TO A PULMONARY INVOLVEMENT BUT WITH NO DEFINITE CLINICAL EVIDENCE OF PERITONEAL INFLAMMATION

CASE 1.—*General pneumococcus infection of all the serous membranes, the meninges, the pleura, the pericardium and the peritoneum.*

A female child, age 16 months, entered the hospital June 19, 1919, with signs of empyema. Drainge of the chest was instituted at entrance and culture of the pus from the empyema showed pneumococci. After the operation the child continued to have a fever. The day before her death, twenty-three days after admission, signs of a meningitis developed and a lumbar puncture revealed a turbid spinal fluid in which pneumococci were found. There were no signs noted referable to the abdomen. The necropsy showed the child to have besides the pneumococcus meningitis and the empyema, a purulent pericarditis and a fibrinopurulent peritonitis. Smear and culture from each of the cavities showed pneumococci.

CASES 2 and 3.—*Pneumococcus infection of the pleura, the pericardium and the peritoneum, but not of the meninges.*

A boy, 2 years old, entered the hospital Oct. 29, 1907, with signs of an empyema. Pus from the chest showed pneumococci. He was in the hospital fifty-four days. There was no vomiting, no abdominal tenderness or distention. The necropsy showed a general purulent peritonitis. The cavity not only contained pus, but the intestines were matted together in many places by an exudate of fibrin. In this case there was also a purulent pneumococcus pericarditis complicating the empyema.

A boy, aged 13 months, came into the hospital April 10, 1920. Physical examination revealed a fibrinous pleurisy. The heart sounds were distant, but pulse was regular and full. The abdomen was negative and there was no vomiting. The child died the sixth day after admission. Necropsy showed a bronchopneumonia with a greatly thickened pleura, an adhesive pericarditis and a general purulent peritonitis. Culture of each showed pneumococci.

It is noteworthy that in each of these three children all or nearly all of the serous membranes of the body were infected. This widespread pneumococcus infection is a peculiarity of early childhood and occurs not infrequently. The three cases illustrate that a pneumococcus peritonitis may exist and that it may have progressed to the point where adhesions were formed and not produce any symptoms sufficient to attract attention.

In the next group of cases, four in number, the peritonitis was the only complication of the pulmonary involvement; these children lived until abdominal distention was present, or until a complete recovery had taken place. They illustrate the onset of symptoms, although it is evident the disease must have begun previously.

PERITONITIS, SECONDARY TO A PULMONARY INVOLVEMENT AND WITH DEFINITE PERITONEAL SYMPTOMS

CASE 4.—*Peritonitis in which symptoms began with abdominal distention and vomiting three weeks after the onset of pneumonia.*

A male infant, 9 months old, admitted April 2, 1918, three weeks previously had an abrupt onset of cough and fever. These symptoms had continued to admission but were not as severe as at the onset, when the temperature was 104 F. When examined at entrance the abdomen was tense and tender. The child was irritable, drowsy, and apparently acutely toxic. The lungs were negative on physical examination. The leukocyte count was 31,000; 79 per cent. polymorphonuclears. Von Pirquet test was negative. The temperature at entrance was 102 F, which was the average temperature in the three days in the ward. The child vomited almost everything taken and the parents stated that this had been the case for two days previous to admission. The abdomen became more enlarged, but otherwise the symptoms remained practically the same. He died in three days. Necropsy showed a small localized empyema at the base of the right lung and a diffuse purulent peritonitis. The culture from the chest and peritoneum was pneumococcus.

CASE 5.—*Peritonitis in which symptoms began with abdominal distention five weeks after the onset of pneumonia, and three weeks after an operation for empyema.*

Sept. 7, 1911, a boy, aged 2 years, was admitted. Eight weeks before admission he had had an attack of pneumonia. In two weeks this was complicated by an empyema for which he was operated on. Although the operation wound had healed, an afternoon fever had persisted. Three weeks before admission gradual abdominal swelling had begun. Physical examination at entrance showed a distended abdomen. A definite circumscribed mass was easily palpable in the left lower quadrant, which it almost completely filled. Examination of the chest revealed an unresolved pneumonia at the site of the empyema cicatrix. The temperature was normal; the leukocyte count was 14,500; 72 per cent. polymorphonuclears. The child died ten days after admission. A postmortem examination was not allowed, but the abdominal mass was aspirated and 30 c.c. of pus was withdrawn, the culture of which showed pneumococcus. Aspiration of the thorax was negative.

CASE 6.—*Peritonitis in which abdominal symptoms began one week after the onset of pneumonia.*

A boy, 4 years old, entered March 10, 1917, with a history of an acute fever one month before. No diagnosis was made. The fever had subsided in a week, but after this the parents noticed the abdomen began to enlarge. At entrance the abdomen was distended and tender, and there was distinct fluctuation at the umbilicus, below which there was an area of dulness impossible to map out distinctly because of pain to the child. Over the base of the left lung there was dulness and suppressed breathing. The temperature was normal; the leukocyte count was 27,000, 64 per cent polymorphonuclears. Tuberculin skin test was negative. The day after entrance an incision was made through the umbilicus, and nearly a quart of pus was removed. The culture from this showed pneumococcus. Eight days after admission the pulmonary signs had disappeared and the boy made an uneventful recovery.

CASE 7.—*Peritonitis in which symptoms began about a week after the onset of pneumonia.*

A girl, 2½ years old, entered the hospital Jan. 30, 1918, because of enlargement of the abdomen. Six weeks before admission she had had pneumonia. This trouble subsided in five days, and a few days later the abdominal swelling was noticed. This was present to a marked degree at entrance, and there was fluctuation at the umbilicus. A mass which extended across the abdomen midway between the xiphoid and umbilicus was interpreted as being a tuberculous omentum. The physical examination was otherwise negative. The temperature was normal and again the von Pirquet test was negative. The leukocyte count was 15,000; polymorphonuclears 76 per cent. An incision was made at the umbilicus, and 13 ounces of pus was evacuated, which was found to contain pneumococcus. The child nearly recovered in two weeks when she was discharged from the hospital on account of the onset of varicella.

These seven cases indicated what is probably the usual course of a secondary pneumococcus peritonitis. In none of these children was the onset of the peritonitis marked by definite abdominal symptoms. Previous to the time when distention was first noticed there was no tenderness, rigidity, pain, nor was there any vomiting. The infection of the peritoneum may rapidly follow the pulmonary infection, as in Cases 6 and 7, or it may not be present for weeks, as in Case 2. Pneumococcus peritonitis begins in a general inflammation which very quickly becomes localized by the formation of adhesions. While this is taking place, there is usually moderate fever, the abdomen gradually enlarges and occasional attacks of vomiting may occur. Palpation of the abdomen discloses one or more masses which may be met with in any part of the abdomen.

In a diagnosis of this condition, tuberculous peritonitis would certainly have to be excluded. Of first importance is the tuberculin skin reaction. A preceding attack of pneumonia or empyema would suggest that the peritonitis was caused by the pneumococcus. The rapid progress of this disease is not characteristic of tuberculous peritonitis.

A study of these cases shows that in pneumococcus peritonitis the patients rarely die from that disease, but from associated conditions.

The treatment of pneumococcus peritonitis illustrated in these seven cases should be expectant until the inflammatory process has become circumscribed and an abscess is formed. At that time incision and drainage of the abscess is indicated.

IDIOPATHIC PNEUMOCOCCUS PERITONITIS

The so-called idiopathic or primary pneumococcus peritonitis is just as characteristic in its course as the type just discussed. The two cases reported here terminated fatally. Rischbieth and others report

recoveries but they were in older children. It is rare for one of these patients to recover.

CASES 8 AND 9.—*In the following cases neither the history nor the physical examination nor the necropsy showed any disease besides the peritonitis.*

A girl, 2 years and 10 months old, entered the hospital April 24, 1911. Six days before she had had an acute vomiting attack, and became prostrated immediately. She complained of pain in her abdomen which was held rigid. Fever had been varying between 102.5 and 105 F. On the day of entrance, her abdomen was noticeably distended. The physical examination was negative, except for the tender, rigid and distended abdomen. Temperature on admission was 106.4 F. The leukocyte count was 38,000; polymorphonuclears, 88 per cent. The child died six hours after admission. The postmortem examination was negative, except for a general purulent peritonitis. Culture from the peritoneal pus showed pneumococcus.

A girl, 2½ years old, was admitted July 19, 1919. Two days previously she suddenly began to vomit and to complain of pain in her abdomen. The fever was high and there was a diarrhea. From the onset she was acutely toxic. On admission the abdomen was tender everywhere and was held very rigid. The remainder of the examination was negative. Temperature was 102.6 F. In this case there was a leukopenia, the leukocytes numbering only 3,600; polymorphonuclears, 56 per cent. A laparotomy was performed two hours after admission and a purulent peritonitis was found. Culture from the peritoneal exudate showed pneumococcus. The temperature remained elevated, although there was always free drainage from the incision. Other symptoms remained unchanged. She died four days after admission, six days after the onset. The necropsy revealed nothing besides the general purulent peritonitis which, however, showed signs of becoming localized by the formation of adhesions.

These two cases, which in many respects closely resemble each other, enable one to form a distinct clinical picture of this type of pneumococcus peritonitis. The abrupt and stormy onset differs from the very similar peritonitis of streptococcus origin when that is apparently idiopathic. Rabinowitz [7] has reported a number of these cases and he calls attention to this differential point. Clinically, the two conditions are indistinguishable, except that in idiopathic streptococcus peritonitis the onset is more often gradual. Acute appendicitis may simulate primary pneumococcus peritonitis but in this disease the symptoms are not as acute. In appendicitis the temperature usually is lower, and well marked localized tenderness is present.

The treatment of these cases is a debated point. It is the general opinion of writers on this subject that the abdomen should be opened. In Case 8, the child was not operated on and in Case 9 the child was operated on. It is significant that the course of the disease was so similar in these two children and it seems evident that nothing was gained by opening the abdomen. The pathology of the disease suggests the form of treatment. These, as well as cases of the first two groups, early tend to form a localized abscess and apparently opera-

7. Rabinowitz, M. A.: Am. J. M. Sc. **157**:797 (June) 1919.

tion is of no benefit until that localization has taken place. The best treatment would seem to be to keep the patient fully under the influence of morphia and by this method keep the intestines at rest and provide stimulation for the child. If the vomiting is severe, hypodermoclysis is indicated.

I wish to thank Dr. L. Emmett Holt for the privilege of reporting these cases, and for his assistance in the preparation of this paper.

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